
CANADIAN RESPIRATORY JOURNAL

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Volume 11 Supplement B

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State of the Art Compendium: Canadian Thoracic Society recommendations for the management of chronic obstructive pulmonary disease

CTS Review Panel

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Chronic obstructive pulmonary disease (COPD) is a common cause of disability and death in Canada. Moreover, morbidity and mortality from COPD continue to rise, and the economic burden is enormous. The main goal of the Canadian Thoracic Society's evidence-based guidelines is to optimize early diagnosis, prevention and management of COPD in Canada. The main message of the guidelines is that COPD is a preventable and treatable disease. Targeted spirometry is strongly recommended to expedite early diagnosis in smokers and former smokers who develop respiratory symptoms, and who are at risk for COPD. Smoking cessation remains the single most effective intervention to reduce the risk of COPD and to slow its progression. Education, especially self-management plans, are key interventions in COPD. Therapy should be escalated on an individual basis in

accordance with the increasing severity of symptoms and disability. Long-acting anticholinergics and beta-2-agonist inhalers should be prescribed for patients who remain symptomatic despite short-acting bronchodilator therapy. Inhaled steroids should not be used as first line therapy in COPD, but have a role in preventing exacerbations in patients with more advanced disease who suffer recurrent exacerbations. Acute exacerbations of COPD cause significant morbidity and mortality and should be treated promptly with bronchodilators and a short course of oral steroids; antibiotics should be prescribed for purulent exacerbations. Patients with advanced COPD and respiratory failure require a comprehensive management plan that incorporates structured end-of-life care. Management strategies, consisting of combined modern pharmacotherapy and nonpharmacotherapeutic interventions (eg, pulmonary rehabilitation and exercise training) can effectively improve symptoms, activity levels and quality of life, even in patients with severe COPD.

Key Words: Best practice; COPD; Guidelines; Review

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This document is available online at <http://www.lung.ca/cts/guidelines.cfm>

CANADIAN CONSENSUS GUIDELINES FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Canadian Thoracic Society (Ad Hoc Committee on Chronic Obstructive Pulmonary Disease/Rehabilitation)

Objectives

- To review the burden of chronic obstructive pulmonary disease (COPD) in Canada and to review what is known about current ambulatory care management of COPD;
- To develop evidence-based guidelines for optimal management of COPD;
- To provide recommendations based on expert consensus where evidence is lacking;
- To develop strategies for the dissemination and implementation of guidelines at a local level; and
- To identify areas where new research is required, based on scrutiny of the current scientific literature. Future studies might be undertaken by a new network of Canadian COPD researchers.

Target audience

- Family physicians and specialists;
- Health care professionals involved in COPD management; and
- Patients with COPD and their families.

The development process

The Ad Hoc Committee of the Canadian Thoracic Society (CTS) for COPD/Rehabilitation, which was chaired by Dr Denis O'Donnell, created a steering committee for the development of Canadian COPD guidelines. Eleven team leaders were selected and each given the responsibility for creating small expert focal groups to cover particular aspects of COPD management. Where possible, these groups had a broad-based representation of family physicians and nonphysician health care professionals with an interest in COPD. Each team leader was responsible for the preparation of a document on their designated theme. The team leader provided the recommendations of their focal groups, based on a critical review of the scientific literature, and categorized these recommendations on the strength of the scientific evidence supporting them. The team leader also identified contentious areas for wider discussion with the larger consensus group. Thereafter, a meeting of the team leaders was held to revise and refine a first draft of the guidelines. A consensus conference was arranged and comprised all contributors to guideline development (ie, the 11 small focal groups) and other invited experts, with the aim of finalizing a consensus statement for COPD management. Feedback from attendees at this conference was considered during a final meeting of the steering committee and the final document was subsequently produced and submitted for publication.

DEFINITION AND DIAGNOSIS

COPD is a respiratory disorder largely caused by smoking, characterized by progressive, partially reversible airflow obstruction, systemic manifestations, and increasing frequency

and severity of exacerbations (1,2). The cardinal symptoms experienced by patients with COPD are shortness of breath and activity limitation. The symptoms are usually insidious in onset, progressive, and typified by frequent exacerbations. Although initially confined to the lungs, systemic manifestations of skeletal muscle dysfunction (3), right heart failure (4), secondary polycythemia (5), depression (6) and altered nutrition (7) accompany advanced disease.

Objective demonstration of airflow obstruction by spirometry is mandatory for the diagnosis of COPD. All patients with suspected COPD should have their lung function assessed by spirometry. A reduced forced expiratory volume in 1 s (FEV_1) to forced expiratory vital capacity (FVC) ratio indicates obstructive impairment (8). A postbronchodilator FEV_1 of less than 80% of the predicted value, associated with an FEV_1/FVC of less than 0.7, define airflow obstruction, and both are necessary for the diagnosis of COPD to be established. Importantly, they are not fully reversible to normal in COPD. Accordingly, the diagnosis of COPD may require more than one evaluation.

Smoking represents by far the most important risk factor (9). Occupational dusts, noxious fumes and gas exposures are also risk factors for the disease (10,11).

COPD has been called chronic bronchitis or emphysema, but the use of these terms in clinical practice is seldom helpful. Chronic bronchitis is defined as cough and sputum for three months in at least two consecutive years. Emphysema is defined as abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls (1). Chronic bronchitis and emphysema both occur in COPD, but both may also be present in the absence of airflow obstruction and the diagnosis of COPD. COPD does not include airflow obstruction associated with other lung diseases such as cystic fibrosis or diffuse bronchiectasis. Clinically important differences between COPD and asthma are outlined in Table 1.

A clinical suspicion of COPD should be entertained in smokers, especially those with dyspnea, cough, sputum and a history of frequent respiratory infections. COPD can be difficult to diagnose in the absence of objective assessment (12); hence, the requirement for mandatory spirometry.

CLASSIFICATION OF COPD

There are a number of existing COPD classification schemes. These include those of the American Thoracic Society (2), the European Respiratory Society (13), the British Thoracic Society (14) and the Global Initiative for Chronic Obstructive Lung Disease (15). All are based on the FEV_1 as percentage predicted, and each differs from the others. In general, patients with an FEV_1 less than 30% to 40% have 'severe' disease and those with FEV_1 greater than 60% to 70% have 'mild' disease.

These classifications schemes are based on FEV_1 values (in broad terms) that correlate with severity of symptoms (16), mortality (16-19) and the risk of lung cancer (20) (Level 2B). However, there is no clear evidence of a specific threshold effect of FEV_1 on clinical outcomes (Level 2E). Also, other variables are important in determining COPD prognosis; notably, disease-related quality of life, body mass index and blood gases.

TABLE 1
Clinical differences between asthma and chronic obstructive pulmonary disease (COPD)

	Asthma	COPD
Age of onset	Usually <40 years	Usually >40 years
Smoking history	Not causal	Usually >10 pack-years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	Never normalizes
Clinical symptoms	Intermittent and variable	Persistent

TABLE 2
Canadian Thoracic Society chronic obstructive pulmonary disease (COPD) classification*

COPD stage	Symptoms
At risk (does not 'yet' fulfill the diagnosis of COPD)	Asymptomatic smoker, former smoker or chronic cough with sputum, but postbronchodilator $FEV_1/FVC \geq 0.7$ and/or $FEV_1 \geq 80\%$ predicted
Mild	Shortness of breath from COPD [†] when hurrying on the level or walking up a slight hill (MRC 2)
Moderate	Shortness of breath from COPD [†] causing the patient to stop after walking approximately 100 m (or after a few minutes) on the level (MRC 3-4)
Severe	Shortness of breath from COPD [†] resulting in the patient being too breathless to leave the house or breathless after undressing (MRC 5), or presence of chronic respiratory failure or clinical signs of right heart failure

*Postbronchodilator forced expiratory volume in 1s/forced expiratory vital capacity ratio (FEV_1/FVC) of less than 0.7 and FEV_1 less than 80% predicted are both required for the diagnosis of COPD to be established. [†]In the presence of non-COPD conditions that may cause shortness of breath (eg, cardiac dysfunction, anemia, muscle weakness, metabolic disorders), patient symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath. MRC Medical Research Council dyspnea scale

Individual patients should be classified and managed according to their symptoms (Table 2, adapted from a validated dyspnea scale) (21) (Figure 1).

While the CTS COPD classification scheme does not specifically use FEV_1 thresholds, the role of spirometry in the diagnosis and ongoing management of COPD remains essential. Recommendations for assessing the severity of airflow obstruction in COPD are listed in Table 3.

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathogenesis of COPD is imperfectly understood. Current opinion is best summarized by stating that cigarette smoke (22-27) or other noxious inhalants stimulate an inflammatory response in the lung which induces airflow obstruction in susceptible individuals. This process has significant systemic manifestations (28-30) that are most evident late in the disease. Removal of the inciting stimulus is of great benefit early in the process, but may be less effective in late disease (31).

In COPD, chronic inflammation is present in the central airways, peripheral airways, lung parenchyma and pulmonary vasculature. In large airways, inflammatory cells infiltrate the surface epithelium and are associated with hypertrophy and

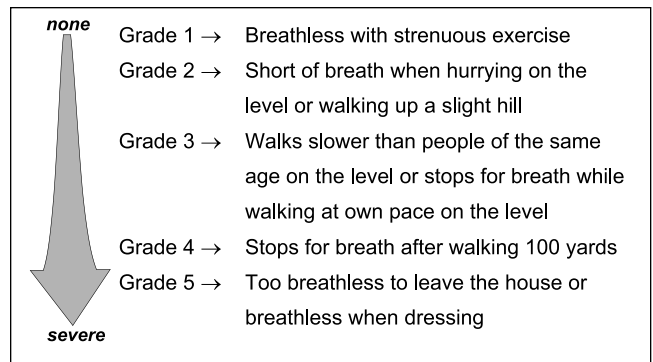


Figure 1) The Medical Research Council dyspnea scale is used to assess shortness of breath and disability in chronic obstructive pulmonary disease. Reproduced from reference 21

TABLE 3
Defining severity of airflow obstruction in chronic obstructive pulmonary disease

Airflow obstruction	Spirometry
Mild	FEV_1 60% to 79% predicted, $FEV_1/FVC < 0.7$
Moderate	FEV_1 40% to 59% predicted, $FEV_1/FVC < 0.7$
Severe	$FEV_1 < 40\%$ predicted, $FEV_1/FVC < 0.7$

FEV_1 Forced expiratory volume in 1 s; FVC Forced expiratory vital capacity

hyperplasia of mucus glands (22,32,33), which form the anatomical basis of chronic cough and sputum. In airways smaller than 2 mm in internal diameter, injury leads to narrow lumens and airway obstruction (34). Destruction of the lung parenchyma in COPD typically occurs as centrilobular emphysema involving dilation and destruction of the respiratory bronchioles (35,36), along with the associated pulmonary capillary bed. These changes also cause airflow limitation. Resulting maldistribution of ventilation and perfusion within the diseased lung give rise to hypoxemia and carbon dioxide retention, which in turn may cause pulmonary hypertension.

These pathological changes in the lungs lead to corresponding physiological changes characteristic of the disease, including airflow obstruction, mucous hypersecretion, ciliary dysfunction, abnormalities in operating lung volumes (ie, lung hyperinflation), pulmonary hypertension and cor pulmonale.

SUMMARY

COPD is a respiratory disorder largely caused by smoking, and is characterized by progressive, partially reversible airflow obstruction, systemic manifestations, and increasing frequency and severity of exacerbations. The cardinal symptoms experienced by patients with COPD are shortness of breath and exercise limitation, which are usually insidious in onset, progressive and typified by frequent exacerbations. The impairment in respiratory function and the systemic manifestations reduce health-related quality of life. COPD should be suspected in patients presenting with dyspnea, cough or sputum production, or in patients with a significant smoking history. Such patients should undergo spirometry, which is mandatory to

make the diagnosis. A postbronchodilator FEV₁ less than 80% of the predicted value, associated with an FEV₁/FVC less than 0.7, define airflow obstruction; both are necessary for the diagnosis of COPD to be established.

KEY MESSAGES

- COPD is defined as a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airflow obstruction, systemic manifestations, and increasing frequency and severity of exacerbations.
- The use of terms such as chronic bronchitis or emphysema should not be used to define COPD, and their use in the clinical management of COPD patients is discouraged.
- COPD is usually suspected in patients presenting with

dyspnea, cough or sputum production, or in patients with a significant smoking history. All patients with suspected COPD should have their lung function assessed by spirometry because objective demonstration of airflow obstruction by spirometry is mandatory for the diagnosis of COPD.

- Airflow obstruction is defined as a postbronchodilator FEV₁ less than 80% of the predicted value, associated with an FEV₁/FVC less than 0.7; both are necessary for the diagnosis of COPD to be established.
- The CTS COPD classification scheme is designed for clinical practice and is symptom-based.
- While the CTS COPD classification scheme does not specifically use FEV₁ thresholds, the role of spirometry in the diagnosis and ongoing management of COPD remains essential.

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EPIDEMIOLOGY OF COPD

Because of its prevalence, morbidity and mortality, COPD accounts for a huge disease burden with consequences for individuals, families, the health care system and taxpayers in Canada.

Prevalence

According to the 2000/01 Canadian Community Health Survey (1), 3.7% of participants over the age of 35 years (600,000 adults) had probable COPD as defined by self-report of either chronic bronchitis with a history of smoking, or emphysema or COPD diagnosed by a health care professional. The prevalence among women and men was similar (3.8% and 3.6%, respectively). The prevalence of probable COPD has been similar since 1994/95, though the questions used to elicit the information have differed somewhat over the years. In 2000/01, the prevalence of probable COPD increased with age for both men and women (Figure 2). Between the ages of 55 and 64 years, men and women had the same prevalence of COPD. Under the age of 55 years, women had a higher prevalence of COPD, while over age 65, men had a higher prevalence than women.

Mortality

In 1999, 9518 Canadians died from COPD – 5544 men and 3974 women. COPD accounted for 4.9% of deaths among men and 3.8% of deaths among women in Canada in 1999, making it the fourth leading cause of death for men and the fifth for women. Overall mortality rates for COPD from 1988 to 1999 have increased; the rate for women has increased by 53% and is still increasing. The rate among men has decreased by 7% and continues to fall. Mortality rates increase rapidly over the age of 75 years.

COPD death rates are almost certainly underestimates. It was shown recently that COPD was mentioned on the death certificates of fewer than 50% of patients with at least one hospitalization for this diagnosis (2). It is very likely that COPD contributed to the death of many of these patients.

The change in the age structure of the population, with an increasing number of people aged over 65, will result in a continued increase in mortality related to COPD. Figure 3 shows the number of COPD deaths, actual and projected, in Canada, from 1987 to 2016. The increasing mortality rates among women compared with men, combined with the higher proportion of women among seniors, will produce a significantly increased number of deaths (and, by proxy, cases) among women in the future.

Quality of life

COPD often has a major negative impact on the patient's functional abilities, and can eventually progress to cause disability (3). According to the 2000/01 Canadian Community Health Survey (1), 35% of individuals with COPD reported that the disease had caused a restriction in their activity at home, at work or elsewhere. Almost 10% (9.7%) reported using home care services. In the Community Health Survey, Canada 2002 (1), patients with COPD rated their health as worse than stroke patients and worse than most of the other chronic diseases including cancer.

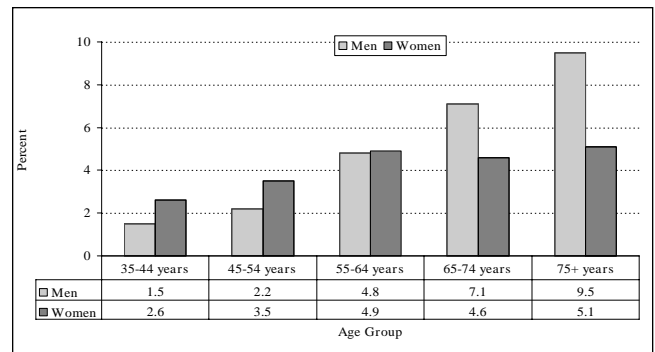


Figure 2) Prevalence of physician-diagnosed chronic bronchitis and emphysema among women and men by age group in Canada, 2000/01

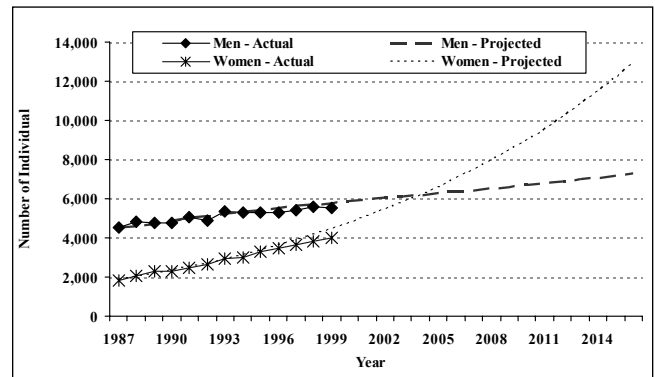


Figure 3) Number of chronic obstructive pulmonary disease deaths, actual and projected, in Canada, from 1987 to 2016. Source: Centre for Chronic Disease Prevention and Control, Health Canada, using data from Mortality Database, Statistics Canada. Population projections from Statistics Canada

The Global Burden of Disease Study (4) estimates the fraction of premature mortality and disability attributable to major disease using a composite score, called the disability-adjusted life year (DALY). The DALY represents the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of that disability. According to some projections, COPD, which ranked 12th in 1990, will be the fifth leading cause of DALYs worldwide in 2020, behind ischemic heart disease, major depression, traffic accidents and cerebrovascular disease.

Health care services

COPD patients require a wide variety of care and services. Acute exacerbations of COPD and their complications, plus comorbid conditions, are major causes of health care use, including hospitalization.

In Canada in 2000/01, COPD was the seventh most common cause of hospitalization for men (2.3%) and the eighth for women (2.0%), excluding childbirth. Beginning at approximately age 55, the hospitalization rates for COPD patients increased steadily with age. Rates are higher for men than women over the age of 65 years (Figure 4). The rates and duration of hospitalization for COPD have been decreasing for men over the past 10 years and for women in the past couple of

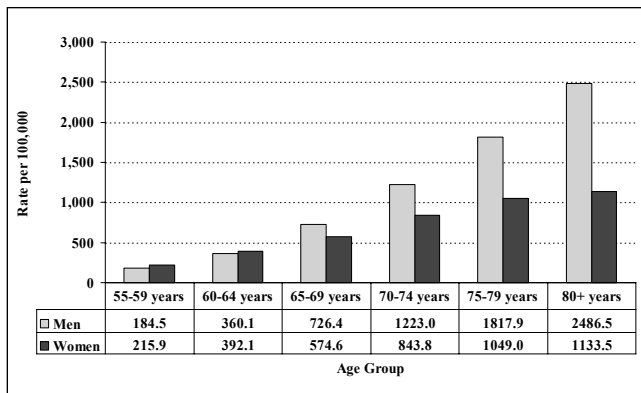


Figure 4) Chronic obstructive pulmonary disease hospitalization rates (per 100,000) by age group and sex in Canada, 2000/01

years, likely due to changes in the delivery of health services. The actual number of hospitalizations had been increasing, but in the past two years, hospitalizations have started to decrease.

The risk of rehospitalization is high among individuals with COPD – 40.3% of men and 36.8% of women who were admitted to hospital in Canada during 1995 were readmitted in the 12 months following their initial admission. The risk of readmission increases with age for both men and women – from 29.5% and 33.5% among men and women, respectively, at the age of 55 to 59 years, to 44.1% and 37.6%, respectively, at the age of 80 to 84 years. The hospitalization of COPD patients, and the phenomenon of multiple hospitalizations, create a major burden on the health care system that will continue into the future.

Economic burden of COPD

COPD has a major impact on health care costs in Canada. A recent Health Canada publication, *The Economic Burden of Illness in Canada 1998* (5), reported that \$467.4 million were spent on hospital and drugs for COPD in 1998. The indirect costs (premature mortality, long- and short-term disability) were even higher at \$1.2 billion (Table 4). These cost estimates do not include physician costs, or costs for other health professionals, rehabilitation or other related health care services. Thus, the actual economic impact is much higher than the \$1.67 billion estimated from this report.

KEY MESSAGES

- Despite a huge disease burden of COPD with consequences for individuals, families, the health care system and taxpayers, this disease receives only minimal attention from the government and the public.

TABLE 4
Selected costs of chronic obstructive pulmonary disease in Canada, 1998 (4)

Component	1998 cost (\$1,000,000)	Percentage of total costs, all diseases
Direct costs	467.4	
Drugs	122.9	2.0
Hospital care	344.5	1.2
Indirect costs	1203.2	
Premature mortality	770.7	2.3
Short term disability	271.7	2.8
Long term disability	160.8	0.5
Total costs	1670.6	

- Prevalence of COPD is likely underestimated because the diagnosis is often made when the patient has advanced disease. As well, the actual number of COPD deaths may be higher because the primary cause of death may be listed as pneumonia or congestive heart failure rather than the underlying cause of COPD.
- Until very recently, COPD was considered a man's disease; this portrait of the disease is changing because recent increases in prevalence and mortality are largely due to increasing rates of COPD among women. Furthermore, the change in the age structure of the population, with an increasing number of people aged over 65, will eventually result in a continued increase in prevalence, mortality and health care services used.
- COPD has a major economic impact in Canada in excess of \$1.67 billion.

Data provided in the text have been adapted from the Centre for Chronic Disease Prevention and Control, Health Canada, Canadian Institute for Health Information (6).

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RISK FACTORS AND PREVENTION, TARGETED TESTING, EARLY DIAGNOSIS

COPD develops in some smokers but not others due to a complex interaction between the susceptible host and its changing environment. Some host factors have been well studied, including alpha-1-antitrypsin (AAT) deficiency, bronchial hyper-responsiveness and a history of childhood viral infections. Environmental risk factors other than exposure to tobacco smoke include occupational exposures and air pollution. There are other potential but less well studied risk factors. This section reviews interactions between host and environment in the development of COPD.

Host factors

AAT deficiency: Severe AAT deficiency predisposes to the development of disabling emphysema in smokers at the relatively young age of approximately 40 years, with few surviving to 60 years (1,2). Severe AAT deficiency is a relatively common inherited disorder occurring in about one in 6000 of the white population in North America (3). Based on this prevalence rate, severe AAT deficiency affects approximately 5000 individuals in Canada, but it is estimated that the diagnosis of deficiency has been made in fewer than 1000 (20%) of these individuals (4). This subject is reviewed in detail in the section: Guidelines for Management of Alpha-1-Antitrypsin Deficiency, page 50B of this report.

Other genetic factors: Family members of COPD patients without AAT deficiency are at increased risk of developing the disease, suggesting inherited risk factors other than AAT deficiency (5-10). Genetic risk factors for COPD have been summarized in a recent review article (11). Genes that may be directly implicated in COPD could be affecting proteolytic enzymes and antiproteases, metabolism of toxic substances in tobacco smoke such as oxidants, the inflammatory response to cigarette smoke, and the efficiency of mucociliary clearance (11). It is likely in the near future that the role of genetic risk factors other than AAT in the development of COPD, particularly in early onset of severe COPD, will be further defined.

Lung growth: Smoking during pregnancy (active or passive exposure) poses a risk for the fetus because it is associated with low birth weight and affects the growth and development of the lungs in utero (12). Exposure to environmental tobacco smoke (ETS) during childhood has been associated with functional impairment and lower than expected increases in lung function during growth (13-16); active smoking also retards the normal increase in expiratory flow that occurs during adolescent growth (17). A clear link between such exposure and COPD has not been established, however.

Childhood viral infections: There is equivocal evidence that a history of viral infections in early childhood predisposes to the development of COPD. Research by Hogg (18) suggests that a specific childhood viral infection (adenovirus) may amplify lung inflammation induced by cigarette smoke and contribute to the pathogenesis of some cases of COPD.

Bronchial hyper-responsiveness: Bronchial hyper-responsiveness (BHR) may predispose a host to the development of fixed airway narrowing, and therefore may be a risk factor for COPD (19). In the Lung Health Study, BHR, after smoking and age, was the third most important independent predictor of declining

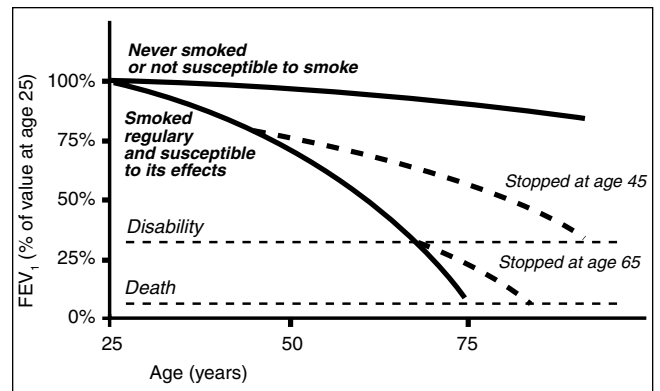


Figure 5) Effects of smoking and stopping smoking on rate of decline of forced expiratory volume in 1 s (FEV_1) (24)

FEV_1 (20,21). Although the mechanism is not known, female smokers have more demonstrable BHR than male smokers (20,21).

Environmental risk factors

Active exposure to tobacco smoke: Cigarette smoking is overwhelmingly the most important etiological agent in the development of COPD (22). Altogether, cigarette smoking accounts for 80% to 90% of COPD cases (23). As illustrated in Figure 5, smokers have a greater rate of decline in FEV_1 compared with age-matched nonsmokers, and the decline is related to smoking intensity (24). Smoking of any type, including light cigarettes (25-28), cigars (29), pipes (30) and marijuana (31), may be associated with inflammatory lung damage similar to that seen in COPD.

Passive exposure to tobacco smoke: Exposure to ETS not only increases the risk of health problems, but also increases the risk of children becoming addicted smokers, because children with parents (32) or siblings (33) who smoke are at increased risk of adopting the smoking behaviour themselves. While environmental exposure to tobacco smoke in the household (34) and workplace (35) has been associated with deterioration in pulmonary function, epidemiological reviews in this area remain inconclusive (36).

Risk factors other than tobacco: In a minority of patients with COPD (10% to 20%), smoking may not be the main cause of the disease (23). Other risk factors, such as exposure to occupational agents and air pollution, may contribute to the development of COPD.

Occupational exposures: Epidemiological studies (37) have provided evidence that exposure to fibrogenic agents (eg, gold, coal, asbestos), as well as complex, mixed exposures (mineral dusts, fumes and gases) may independently cause clinically relevant COPD. Community studies have identified a link between deterioration in lung function and wood smoke (38,39), silica dust, fiberglass dust (40), solvent fumes (40,41) and cadmium (42). Other studies have identified significant correlations with annual lung function loss and exposure to silica, coal, iron and other mineral dusts, nonhalogenated hydrocarbons and turpentine (43,44), sulphur dioxide and the oxides of nitrogen (eg, nitrogen dioxide) (44,45).

Air pollution: 'Smog' (outdoor air pollution) from automobile emissions is a documented source of environmental sulphur dioxide and nitrogen dioxide gas exposure (46). Most studies have shown only minor compromise of lung function by these influences. In developing countries, deterioration in lung function may be associated with indoor air pollution from cooking and heating fires in poorly vented dwellings (38,39).

Other potential risk factors

Other potential risk factors for COPD include ethnicity, sex, socioeconomic status, nutrition and alcohol use. There are no large differences in the effects of cigarette smoking on lung function between ethnic groups (47). There are conflicting studies on the effects of cigarette smoke in females compared with males (41-57). COPD prevalence is increasing in women. This may be related to an increase in smoking rates among women or a biological predisposition.

Lower socioeconomic status may predict decreased levels of lung function in both smokers and nonsmokers (58). It is difficult to separate this from confounding factors such as smoking habits, ETS, industrial exposure and other lifestyle factors. Low body mass index is an independent risk factor for mortality in COPD, and the association is strongest in patients with severe COPD (59,60). The extent to which nutritional factors contribute to the development of COPD is unknown, although lung function has been related to the intake of certain dietary supplements (61-64). Both retrospective and prospective studies have shown a correlation between alcohol consumption and development of COPD, irrespective of age and smoking habits (65), but other confounding factors have not been addressed.

Prevention

Because 80% to 90% of all COPD cases are attributable to tobacco exposure, the disease could largely be prevented if no one smoked. Smoking cessation has been identified as the single most important modifiable health behaviour for preventing or slowing the progression of COPD (66,67), and is covered in the section entitled 'Smoking Cessation in COPD' on page 20B of this document.

Targeted testing and early diagnosis

The value of screening for COPD continues to be widely debated at this time. The purpose of a screening program is to identify people who are asymptomatic but who have abnormalities that signify underlying disease. Spirometry has been proposed as a screening test for COPD in all smokers. There is a lack of high quality evidence to support the benefits of widespread screening for COPD because the effectiveness of a positive spirometric result in increasing smoking cessation has not been demonstrated, nor has the cost benefit of spirometry been assessed. Mass screening of asymptomatic individuals for COPD is not supported by the current evidence and therefore is not recommended. Performing targeted spirometric testing or case selection to establish early diagnosis in individuals at risk for COPD should be considered if the test is done well, and if the health care professional is willing and able to provide advice and intensive smoking cessation counselling.

Clinical assessment

History: Clinical assessment begins with a thorough history. Tobacco consumption should be quantified. Careful assessment of symptoms and the resulting disability should follow. A series of probing questions is often required to uncover the true extent of breathing difficulty and exercise curtailment that the patient experiences. Severity of breathlessness is usually assessed by determining the magnitude of the task (or daily activity) required to precipitate breathing discomfort. The Panel advocates the Medical Research Council dyspnea scale for this purpose (21) (Figure 1).

The history should also include an assessment of the frequency and severity of exacerbations, because this information may guide treatment choices. Other important details that should be extracted are occupational exposures to other lung irritants, family history of COPD or the presence of other chronic respiratory disease. The history should include an inquiry about symptoms that suggest other common comorbidities (ie, heart and circulatory diseases, anxiety and depression). The appropriateness of current medical treatment should be reviewed.

Physical examination: Physical examination of patients with COPD, although important, is not usually diagnostic; even careful physical examination can underestimate the presence of significant airflow limitation. With more advanced disease, signs of lung hyperinflation, right heart failure and generalized muscle wasting may be evident.

Investigations: Pulmonary function testing remains the best objective measurement of pulmonary impairment. Chest x-rays are not diagnostic for COPD, but are often required to rule out comorbidities. This also applies to high resolution computerized tomography scanning, which is not routinely required. Arterial blood gas measurements should be offered to patients with an FEV₁ of less than 40% predicted (if they have low arterial oxygen saturation [SaO₂] on oximetry) or in patients in whom respiratory failure is suspected.

KEY MESSAGES/RECOMMENDATIONS

Risk factors for COPD

Host factors

- AAT deficiency and its association with emphysema are well established (Level 1A).
- Family members of COPD patients with AAT deficiency are at an increased risk of developing the disease (Level 1A).
- Other genetic factors are likely important in the development of COPD (Level 2B).
- Passive exposure to environmental tobacco smoke during gestation and childhood may affect lung growth and lead to reduced maximal lung function (Level 3B).
- Bronchial hyper-responsiveness, after smoking and age, is the third most important independent predictor of declining FEV₁ (Level 2A).

Environmental risk factors

- Active exposure to tobacco smoke is the most important independent risk factor for airflow obstruction, with 80% to 90% of all cases of COPD occurring in cigarette smokers (Level 1A).

- Smoking cessation has been identified as the single most important modifiable health behaviour for preventing or slowing the progression of COPD (Level 1A).
- If the individual with early COPD stops smoking, the natural history of the disease changes due to a slowing of disease progression, and the risk of developing other chronic illnesses (eg, heart disease, lung cancer) is reduced (Level 2A).
- Environmental exposure to tobacco smoke in the household and workplace has been associated with deterioration in pulmonary function (Level 2A).
- Epidemiological studies have provided evidence that exposure to fibrogenic agents (eg, gold, coal, asbestos) and complex mixed exposures (mineral dusts, fumes and gases) may independently cause clinically relevant COPD (Level 2A).
- There may be increased prevalence of chronic bronchitis in cities heavily polluted with coal and in developing

countries; deterioration in lung function may be associated with indoor air pollution from cooking and heating fires (Level 2B).

Prevention

- Preventing the onset of smoking is the most important long-term strategy to reduce the incidence of COPD (and other chronic diseases) (Level 3A).
- Smoking cessation will reduce the risk of COPD and delay disease progression once it occurs (Level 1A).

Targeted testing and early diagnosis of COPD

- Evidence does not support population screening using office spirometry to detect COPD (Level 2C).
- Targeted testing of symptomatic individuals at risk for the development of COPD with intensive smoking cessation counselling can change the progression of disease and delay onset (Level 1A).

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EDUCATION AND COLLABORATIVE SELF-MANAGEMENT IN COPD

The essential role of education in COPD management

Like many chronic illnesses, COPD progressively imposes both physiological and psychological burdens that combine to result in an overall deterioration in the patient's quality of life. As in all chronic disease, the patient is dependent on his or her own resources most of the time. Implementing a self-management approach can achieve significant improvements in patient function and well being, and this can only be done with education. There is wide consensus among experts that patient education is a vital part of COPD management (1,2). Unfortunately, there is ample evidence that Canadian COPD patients are not well informed about their illness, its severity and its management (3).

What are patient self-management, and patient and health care worker education?

The terms self-management and self-management education suggest a more comprehensive approach to patient education and disease management (4). Whereas traditional patient education imparts disease-specific information and technical skills (eg, inhaler technique), self-management education is different in that it teaches patients to identify problems both related and unrelated to the disease, and gives them the skills to solve them. Patient education is essential to effective self-management and helps patients develop living patterns that can incorporate self-management. The aim is to teach methods that can be easily integrated into the patient's lifestyle. They learn what to focus on and what to ignore. They learn what local community resources are available to assist with self-management of COPD. Behaviour modification is an essential component of successful self-management education, and helps incorporate self-management as a part of the patient's normal lifestyle.

Table 5 lists the essential requirements for a successful patient/family and health care professional educational partnership that promotes self-management in COPD. Good communication is fundamental for both patients and health care workers (5,6). The traditional, physician-centred approach emphasizes the physician's perspective on COPD management, which tends to be disease-focused (eg, the irreversible and progressive nature of airflow obstruction, drug therapy, etc), rather than patient-focused. On the other hand, from the patient's perspective, the main issues are related to the impact that COPD has on their day-to-day lives (eg, breathlessness, reduced exercise tolerance, fear, depression, stress on family, etc). Physicians should acknowledge and assist patients' self-management by establishing a framework for collaborative care.

Similarly, patients need to acquire certain skills that will enhance their ability to participate in a collaborative care strategy that values self-management. Patients should be encouraged to ask for and obtain specific self-management advice on how to make lifestyle and treatment changes in appropriate circumstances. They also need practical advice on how to access local community resources, support groups, etc, to assist with disease self-management. Several patient-oriented packages of educational materials for COPD patients are available (7,8).

TABLE 5
Essential requirements for a successful patient/family and health care professional educational partnership that promotes self-management in chronic obstructive pulmonary disease (COPD)

General elements	
Good communication	
Desire on the part of the patient to take control of his or her own condition and practice self-management	
A willingness on the part of health care professional to help empower the patient to collaborative self-management	
Willingness of the patient to effect behavioural change (eg, quit smoking, exercise regularly)	
Ability of the health care professional to assist and support behavioural changes in the patient	
Ability of the patient and family to openly address concerns, fears and conflicts, and the willingness to seek help	
Ability of the health care professional to elicit the patient's true concerns and fears (eg, being a burden on family)	
Willingness and ability of the health care professional to discuss end-of-life issues with the patient and family	
Awareness by all of local community resources (eg, COPD educator, pulmonary rehabilitation programs, local social support networks, palliative care services)	
Awareness of and access to written, video and Web-based educational resources about COPD	
COPD-specific elements	
Knowledge about the nature of COPD and the difference from asthma	
Knowledge of up-to-date drug therapy options including good inhaler technique	
Awareness of the important role of nondrug therapy including:	
<ul style="list-style-type: none"> • Regular exercise • Good nutritional practices • Breathing exercises • Chest clearance techniques • Relaxation techniques • Coping skills • Activities of daily living skills • Psychosocial support skills 	
A patient-focused management strategy (eg, focus on relief of symptoms and psychosocial issues rather than a disease-focused approach)	

What is the evidence that patient education and self-management work in the management of COPD?

Patient and family education are important elements of pulmonary rehabilitation programs, which are widely recognized as successful. However, with the exception of exercise training, which was considered essential, the contribution of other program components, including education, is uncertain (9). Patient education alone (ie, not as part of a comprehensive pulmonary rehabilitation program) has been shown to have a statistically significant effect on inhaler technique, but only a nonsignificant beneficial effect on health resource use and adherence to treatment regimen. However, evidence supporting the more comprehensive self-management educational approach is more encouraging, as is outlined below.

Health-related quality of life

Self-management education in COPD can improve health-related quality of life (HRQoL) and health status (Level 1A): A number of high quality clinical trials have shown that patient education improved COPD-specific HRQoL, as assessed using the St George's Respiratory Questionnaire (SGRQ) (10-13). Results using less specific measures of quality of life such as the Sickness Impact Profile have been conflicting. Behavioural modification, in addition to education in patients with COPD, has been shown to further improve quality of life (14).

Symptoms

Evidence supporting a role for self-management education in reducing symptoms in COPD is inconclusive: The effects of self-management education on COPD symptoms have been examined in several studies (15,16), with conflicting results.

Health care resource use

Self-management education interventions can reduce health care resource use (Level 1A): Bourbeau et al (13) recently reported the results of a well-designed trial of an intensive, comprehensive self-management program including breathing, coughing and inhaler techniques, action plans for exacerbations, lifestyle advice and a home exercise program. Quality of life improved, and hospital admissions for COPD exacerbations and other health problems were reduced by more than 40%. Emergency department and unscheduled physician visits were also reduced by similar amounts in the self-management education group. Savings due to decreased use more than offset the cost of the program. Other trials (17-19) have shown trends of the same kind with smaller effect sizes, perhaps because the interventions were less intense; one trial also demonstrated cost savings (20).

Frequency and management of COPD exacerbations

Self-management education may be associated with a reduction in the frequency of COPD exacerbations (Level 1C) but does improve patient management of exacerbations (Level 1B): The frequency of exacerbations is a difficult outcome measure to study with confidence because it is highly dependent on the definition of a COPD exacerbation; in many studies, COPD exacerbation is defined according to health care use (see above). There have been reports of reductions in exacerbation frequency by self-management programs (10), but these data are probably less important than evidence that self-management plans induce appropriate behaviour among patients when exacerbations occur (12,17,21), presumably due to the action plans embedded in the education program.

Lung function and exercise capacity

Self-management education does not improve lung function but can improve adherence to a regular exercise program for patients with COPD (Level 1C): One would not expect lung function to improve significantly in response to a self-management education program, unless the program is accompanied by significant improvements in effective pharmacotherapy of COPD, and there is no good evidence that this is the case.

Education alone might be expected to motivate some COPD patients to exercise more regularly and thus improve exercise capacity, but this has been difficult to demonstrate. However, most trials have compared education with exercise training and, not surprisingly, favoured exercise training. On the other hand, in one study (22), behaviour modification significantly improved adherence to a home exercise program and improved exercise capacity.

Patient satisfaction

Self-management education is associated with improved patient satisfaction with health care workers (Level 1B): Patient satisfaction with their care is, or should be, important to physicians. There is good evidence that self-management education programs increase such satisfaction (23). This effect may explain some of the other positive effects of patient education noted above.

Summary

This review indicates that patient education is valuable for patients with COPD; in particular, use of a structured and comprehensive self-management education program is most likely to provide the greatest benefits (including improved HRQoL and patient satisfaction, reduced health care use, improved self-management of exacerbations and perhaps reduction in exacerbations). Adherence to exercise programs may also be increased.

RECOMMENDATIONS

1. Education of the patient, the family, the public and health care professionals is valuable and should be part of the continuum of optimal COPD management in Canada (Level 1B). Educational content should include:
 - Identification and modification of risk factors (eg, smoking cessation)
 - Prevention strategies
 - Knowledge of drug therapy options including good inhaler technique
 - Awareness of the role of nondrug therapy including
 - Regular exercise
 - Good nutritional practices
 - Breathing exercises
 - Chest clearance techniques
 - Relaxation techniques
 - Coping skills
 - Activities of daily living skills
 - Patient-focused educational content including a focus on symptoms rather than disease, and end-of-life decision-making issues
 - Awareness of warning signs of a COPD exacerbation and an action plan for initial management of exacerbations
 - Communication skills
 - Awareness of local community resources (eg, COPD educator, Lung Association BreathWorks program [Canadian Lung Association, Ottawa]).

2. The development of a national program for certification of 'COPD educators' is recommended (Level 3).
3. An inventory of national, regional and local COPD educational and rehabilitation programs should be compiled and made available to health care professionals and patients with COPD (Level 3).
4. An inventory of patient education resources including written and Web-based material should be compiled and incorporated into COPD guideline implementation strategies (Level 3).

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SMOKING CESSATION IN COPD

In 2000/01, 25.9% of Canadians aged 12 and over still smoked, with the highest percentage of smokers (35%) aged 20 to 24 years (1). Cigarette smoking is the single most important cause of COPD; the greater the exposure, the greater the risk of developing airways obstruction. The accelerated loss of FEV₁ in susceptible smokers leads to clinically significant COPD in a significant proportion of smokers. COPD is responsible for some 7000 of the 45,000 deaths caused by tobacco use in Canada each year (2). While quitting smoking produces only a small improvement in FEV₁, the subsequent rate of decline returns towards that of a nonsmoker, thus helping to avoid disability and death due to lung disease (Figure 6) (3-7). Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and to stop its progression. Quitting smoking will also result in symptomatic relief of chronic cough, expectoration, shortness of breath and wheezing while reducing the risk of cardiovascular diseases and cancer of the lung and other organs (8,9).

After tobacco, cannabis is the most commonly smoked substance. Marijuana smokers smoke less frequently than most tobacco users. The smoke from the two products contains many of the same respiratory irritants and carcinogens. Health care professionals should advise their patients that the respiratory risks of smoking marijuana are potentially as great as tobacco and are additive to those of tobacco smoking.

Nicotine addiction is responsible for maintaining smoking behaviour while some 4000 other compounds present in tobacco smoke contribute to various diseases (10,11). Several pieces of evidence suggest that smokers vary in their underlying genetic susceptibility to become addicted (10,11). While approximately 46% of smokers try to quit each year, only about 7% are still abstinent a year later. Many smokers cycle through relapses and remissions, reflecting the chronic nature of addiction. At least 70% of smokers visit a physician each year and advice by a physician is considered an important motivator to quit (12).

Advice by physicians and/or nonphysician clinicians, and individual and group counselling have been shown to increase cessation rates. The counselling session length, the number of sessions and the total person-to-person contact time spent with a smoker increase smoking cessation rates (Figure 7). Discussing high risk situations, developing coping skills and preparing for potential relapse also increase smoking cessation rates, as do social support (eg, friend or relative) and intra-treatment support provided by a clinician. Use of medication to assist patients, including nicotine replacement therapy and the antidepressant bupropion, approximately doubles smoking cessation rates. There is insufficient evidence to support hypnosis or acupuncture in smoking cessation. Even minimal interventions, lasting less than 3 min, should be offered to every smoker with the understanding that more intensive therapy resulting in the highest quitting rates should be used whenever possible (12). The same smoking cessation treatments are effective in both men and women. However, women face different psychological stressors and barriers to quitting smoking including an increased likelihood of depression and concerns about weight control that need to be specifically addressed (12). Women considering pregnancy and all smoking parents must be made aware that second hand smoke may have adverse

effects on their children's health, and they should be assisted to stop smoking (13).

Intensive smoking cessation counselling was assessed in the Lung Health Study (7,8), where special care intervention (including behaviour modification techniques and the use of nicotine gum) comprised a 12-session group intervention program over a 10-week period. The patients were followed every four months for five years, with an extended program for those who were unsuccessful or relapsed. The intervention produced a 35% quit rate at some time during the five-year period, compared with 20% in the usual care group; 22% of the special care group and 5% of the usual care group abstained for five years.

Bupropion has been shown to be an effective means to help patients with mild-to-moderate COPD quit smoking (14). In a double-blind, placebo-controlled study of 405 patients with emphysema and chronic bronchitis, 16% of the patients who took bupropion during the 12-week study were continuously tobacco-free between weeks 4 to 26 of the study compared with 9% of those taking placebo. All patients received counselling to help them quit.

Managing tobacco addiction

Recommendations issued to integrate quick, effective smoking cessation counselling into clinical practice can be summarized as follows:

- Ask all patients whether they smoke or have ever smoked, and identify the smoking status in their medical record to promote interventions.
- Assess their readiness to quit.
- Advise repeatedly to stop smoking.
- Assist in progress towards quitting (15-23).

Change in behaviour has been described as proceeding through five stages ranging from precontemplation (not considering stopping in the next six months); contemplation (thinking about stopping within six months); preparation (having decided to stop within the next month); action (having stopped); and maintenance (not having smoked for six months or more). Interventions tailored to this model have received empirical support as an aid to help health professionals assist smokers in the cessation process (15,16,19-23).

Some 85% of smokers are not ready to quit. In **precontemplation** phase, the goal is to help the smoker start thinking about quitting by asking open ended questions about what he or she likes and dislikes about smoking. Advice should be personalized around the risks and rewards relevant to the patient. The patient should be offered support and be provided with educational material. In **contemplation** phase, the goal is to assist the smoker in making the decision to stop. Asking about the benefits and disadvantages of stopping can identify the patient's concerns about quitting. Severe withdrawal symptoms, depression or weight gain experienced in the past may discourage the smoker from making another attempt to quit. The health care professional should suggest strategies to deal with the foreseen difficulties, offer educational material and provide a community resources list.

Approximately 15% of all smokers are ready to stop and are in **preparation** phase. They should be assisted in setting a target date for quitting and by discussing concerns such as withdrawal

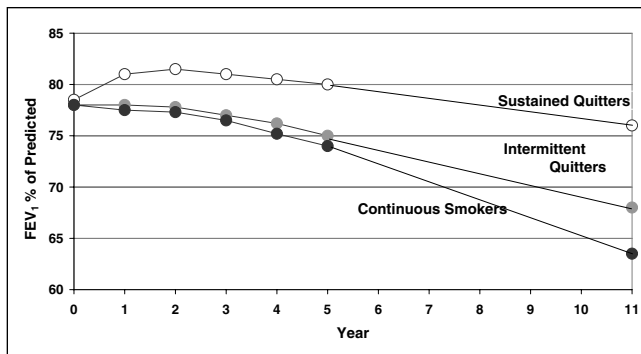


Figure 6) Effects of smoking and smoking cessation on forced expiratory volume in 1 s (FEV₁) decline. Reproduced from (7) with permission

symptoms, weight gain, social relationships, triggers for smoking and increased stress. It is important to help the smoker to plan strategies to use when faced with difficult situations: avoiding places where smokers tend to congregate and altering habits associated with circumstances that trigger the desire to smoke (such as waking up in the morning, after meals or when drinking alcoholic beverages). Drinking water, doing some physical activity and delaying are all ways to curb the strong desire to smoke. An initial weight gain of 2 kg to 4 kg is to be expected as a result of both the slower metabolism as nicotine is withdrawn from the system and the almost universal tendency to cope with stress relief through eating. Because dieting, in addition to smoking cessation, decreases the chances of successfully quitting, patients should be encouraged to maintain a balanced diet and to increase physical activity, as a healthier lifestyle approach to stress relief.

All suitable patients should be encouraged to consider using effective pharmacotherapy for smoking cessation. Special consideration is required for patients with medical contraindications, those who smoke fewer than 10 cigarettes a day, for pregnant or breastfeeding women and adolescent smokers. Medication alleviates nicotine withdrawal symptoms that peak in the first 48 h and eventually subside (12) while the quitter works on other aspects of his or her smoking addiction and learns to cope with triggers to smoke. Nicotine replacement therapy in the form of gum or a transdermal patch, and the antidepressant bupropion hydrochloride, are approved means of smoking cessation therapy in Canada. The choice of medication is a matter of the patient's personal preference, medication availability, past experience, medical history and the presence of contraindications (24-29) (Table 6).

Two published studies (12,30) have demonstrated the efficacy of nortriptyline in smoking cessation. Although not yet approved in Canada or in the United States for that indication (12,30), it is recommended as second line therapy in the United States Department of Health guidelines (12). Treatment is initiated 10 to 28 days before the quit date, to reach steady state, at 25 mg/day with progressive increase to 100 mg/day for approximately 12 weeks. Most common side effects include sedation, dry mouth, blurred vision, urinary retention, light headedness and shaky hands (12).

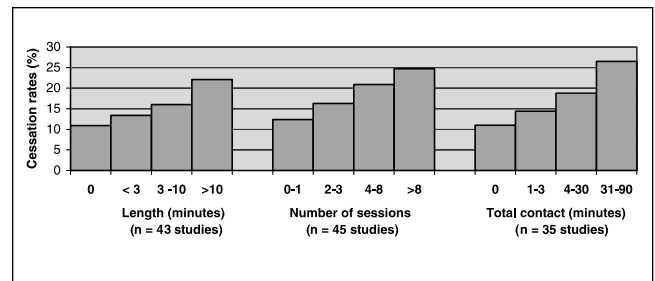


Figure 7) Smoking cessation rates at five months or more according to characteristic of intervention. Adapted from (12)

Contraindications are hypersensitivity to the drug, recovery from acute myocardial infarction or monoamine oxidase inhibitor use within 14 days, and pregnancy (because there is positive evidence of fetal risk) (12). Caution is advised with a history of urinary retention, glaucoma and seizure disorder. Because of the risk of arrhythmias, extreme caution is advised in patients with cardiovascular disease and those at risk of overdose.

The smoker who has stopped and who is in **action** phase should be congratulated and supported. Inquiry about withdrawal, cravings and the effects of the medication should take place regularly. Medication dosages should be adjusted as necessary. The health care professional should discuss the patient's urges to smoke and review difficult social and emotional situations. Praise and encouragement of any success in avoiding smoking for a given period of time should be provided. The health care professional should also discuss slips where one or more cigarettes were smoked without resuming habitual smoking, and the circumstances when they occurred to help the patient find new strategies to deal with those situations. Relapses are a natural part of the smoking cessation process. The circumstances leading to relapse deserve to be discussed to prepare for future similar situations, along with a review of the reasons that motivated the smoker to quit initially.

The **maintenance** phase begins six months after cessation. The desire to smoke persists for a long time and one cigarette is all it takes to start all over for many exsmokers. Strategies to deal with difficult circumstances need to be planned. Reviewing the reasons to quit, discussing actual and future benefits and encouraging lifestyle changes are helpful. Avoiding difficult situations and places, improving stress management skills, obtaining support from family and friends, and paying attention to diet and exercise are all ways to improve the chances of remaining smoke-free.

All health care professionals have a responsibility toward the victims of the tobacco epidemic. Treating tobacco use constitutes the appropriate standard of care. It is essential to ensure that clinicians have the training and support to achieve consistent and effective interventions with tobacco users. Besides helping patients with smoking cessation, health care professionals can play a vital role in combating this massive public health problem. Regarded as the most reliable source of advice and information on health issues, health care professionals must become advocates of tobacco control. Legislation banning tobacco promotion, eliminating smoking in public places, raising cigarette prices through taxation, informing the public about health risks and litigating against the tobacco

TABLE 6
Pharmacological aids to smoking cessation

Drug	Dosage	Duration and other instructions	Contraindications	Adverse effects
Nicotine gum	1 gum/h or as needed	Chew two to three times and park gum between gingiva and cheek for 30 s to 60 s; repeat process for 30 min	Recent myocardial infarction*	Burning
Nicorette	2 mg gum if <25 cigarettes/day, maximum 24/day	Do not eat or drink 15 min before or after use to allow nicotine absorption	Unstable angina*	Jaw pain
Nicorette Plus	4 mg gum if ≥25 cigarettes/day, maximum 24/day	Duration: up to 12 h or as needed Product delays weight gain during use	Severe cardiac arrhythmia* Recent stroke Pregnancy and breastfeeding† Patients under 18 years of age	Hiccups
Nicotine patch	21 mg/24 h,	Place patch on relatively hairless location, typically between neck and waist	Recent myocardial infarction*	Local skin reaction
Nicoderm or Habitrol	14 mg/24 h, or 7 mg/24 h If <10 cigarettes/day, start with lower dose	Duration: four weeks for 21 mg/24 h dose, two weeks for 14 mg/24 h or 7 mg/24 h doses Tapering and duration should be individualized	Unstable angina* Severe cardiac arrhythmia* Recent stroke Pregnancy and breastfeeding† Patients <18 years of age Allergy to tape Generalized skin disease	Vivid dreams
Bupropion	150 mg PO QAM × three days,	Duration: Seven to 12 weeks	Current seizure disorder	Insomnia
Zyban	150 mg PO BID thereafter Leave at least 8 h between two successive doses In case of insomnia, second dose should not be taken close to bedtime; if insomnia persists, reduce dosage to 150 mg every morning Decrease dosage with hepatic or renal failure	Smoking cessation is advised between days 8 and 14 Monitor blood pressure if used with NRT Consider longer treatment for smokers who are subject to significant mood swings or who continue to experience strong urges to smoke after discontinuing bupropion Product decreases weight gain during use	Current or prior diagnosis of bulimia or anorexia nervosa Use of another medication containing bupropion, such as the antidepressant, Wellbutrin Undergoing abrupt withdrawal from alcohol or benzodiazepines, or other sedatives Known hypersensitivity to bupropion Current use of antidepressants of the monoamine oxidase inhibitor thioridazine within 14 days of discontinuation Not recommended in patients with severe hepatic impairment Use caution in situations that may reduce seizure threshold‡ and drug interactions§	Dry mouth Tremors Skin rash Serious allergic reactions

*Nicotine replacement therapy (NRT) should be used with caution among particular cardiovascular patient groups: those in the immediate (within two weeks) post-myocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina pectoris (12). †Many experts believe that the use of NRT is preferable to smoking during pregnancy and lactation; such women should be encouraged to quit first without nicotine replacement and to use it only if the increased likelihood of stopping with its potential benefits outweighs the risk of nicotine replacement and concomitant smoking. Use lowest dose possible, remove patch at night (12,25). ‡History of head trauma or prior seizures, central nervous system tumour, excessive use of alcohol, addiction to opiates, cocaine or stimulants, use of over-the-counter stimulants or anorectics, diabetes treated with hypoglycemics or insulin, medications that lower the seizure threshold (theophylline, systemic steroids, antipsychotics and antidepressants, quinolones, antimalarials, lithium, amantadine, levodopa) (12,26-29), St John's wort (15). §See product monograph for complete list of possible drug interactions. Habitrol: Novartis Consumer Health Canada Inc; Nicorette and Nicoderm: Pharmacia Canada Inc; Wellbutrin: GlaxoSmithKline; Zyban: GlaxoSmithKline Inc. BID Twice daily; PO By mouth; QAM Every morning

industry are all key components of tobacco control policies that health care professionals should be advocating (31).

SUMMARY OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

1. Cigarette smoking is the single most important cause of COPD: the greater the exposure, the greater the risk of developing airways obstruction (Level 1A).
2. Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and to stop its progression (Level 1A).
3. Advice by physicians (Level 1A) and nonphysician clinicians (Level 2A), and individual and group counselling (Level 1A) have been shown to increase cessation rates.
4. The session length, number of sessions and total person-to-person contact time spent with a smoker increase cessation rates over no intervention (Level 1A).
5. Use of stop smoking medication including nicotine replacement therapy and the antidepressant bupropion approximately doubles cessation rates (Level 1A).

6. Discussing high risk situations, developing coping skills and anticipating relapse all increase smoking cessation rates. Intra-treatment support provided by a clinician and extra treatment and social support from a suitable social environment all help with smoking cessation (Level 2A).
7. Even minimal interventions (counselling), lasting less than 3 min, should be offered to every smoker with the understanding that more intensive therapy resulting in the highest quitting rates should be used whenever possible (Level 1A).
8. Health care professionals should advise their patients about the respiratory risks of smoking cannabis, which are potentially as great as and additive to tobacco use (Level 2A).
9. Besides helping patients in smoking cessation, health care professionals should play a vital role in combating the tobacco epidemic. Regarded as the most reliable sources of advice and information on health issues, health care professionals must become advocates of tobacco control (Level 3A).

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PHARMACOLOGICAL THERAPY OF COPD

The goals of pharmacological therapy in COPD should be to control symptoms, improve exercise tolerance, improve health status, reduce the frequency and severity of exacerbations, and slow the decline in pulmonary function.

Bronchodilators

Bronchodilators currently form the mainstay of pharmacological therapy of COPD. They work by decreasing airway smooth muscle tone, thus improving expiratory flow and lung emptying. Inhaled therapy is preferable to oral therapy because inhaled drugs target the airway directly and are less likely to cause systemic adverse effects. There are three major classes of bronchodilators available for use in COPD: anticholinergics, beta-2-agonists and methylxanthines. All three classes include drugs that are short or long acting. In addition, bronchodilators can be combined with one another or with inhaled corticosteroids in one formulation. Published trials on bronchodilators in COPD have relied on a variety of different outcome measures or end points to demonstrate therapeutic benefit, as reviewed below.

Pulmonary function: The traditionally measured end point in COPD is FEV₁. Spirometric measurements, including FEV₁, have the benefit of being widely available, reproducible and simple to obtain. The response of FEV₁ to bronchodilator therapy in patients with COPD is often very modest, and for individual patients, a lack of change in FEV₁ in COPD does not exclude benefit from bronchodilator therapy (1,2). Bronchodilators may produce reductions in residual volume and functional residual capacity, although there are minimal changes in the FEV₁ (3,4). Reduced lung volumes following use of bronchodilators are clinically important because they relate to reduced dyspnea and increased exercise intolerance (1,2).

Exercise testing: As noted above, bronchodilation reduces air trapping and dynamic lung hyperinflation during exercise. This is associated with increased ventilatory capacity and increased exercise performance due to reduced dyspnea. Exercise tests range from relatively simple walk tests to more extensive cardiopulmonary exercise tests. Walk tests, such as the 6 min walk (where the patient is instructed to walk as far as possible within 6 min) require few resources and provide a reproducible measure of overall functional capacity. However, walk distance is a poor measure of bronchodilator effectiveness, compared with other forms of exercise testing (5). Constant load cycle exercise testing at 60% to 75% of patient maximal work capacity appears to be more sensitive than field tests (5).

Dyspnea and quality of life: Numerous scales have been developed to quantify the impact of an intervention on dyspnea and quality of life. Frequently used scales include the baseline dyspnea index and transitional dyspnea index (TDI) which measure dyspnea and changes in dyspnea, respectively, as well as the chronic respiratory disease questionnaire and the SGRQ, which both measure quality of life (6-8).

The evidence supporting the use of bronchodilators in COPD is summarized below using the end points outlined above.

Anticholinergics

Bronchodilating actions of anticholinergics: Human airways are innervated by a generous supply of efferent, cholinergic, parasympathetic autonomic nerves. The release of acetylcholine at these sites results in stimulation of muscarinic receptors, and subsequent airway smooth muscle contraction and release of secretions from the submucosal airways glands (9). Ipratropium, and its long-acting relative tiotropium, exert bronchodilating action because of their antimuscarinic properties (10-13). These drugs antagonize the actions of acetylcholine at parasympathetic, postganglionic, effector-cell junctions by competing with acetylcholine, resulting in airway smooth muscle relaxation and bronchodilation (10).

Adverse effects of anticholinergics: Inhaled anticholinergic drugs are generally well tolerated. A bitter taste and dry mouth have been reported (13). Occasional prostatic symptoms with urinary retention have also been reported. Use of wet nebulizer solutions with a face mask can precipitate acute glaucoma if the drug gets directly into the eye. All of these side effects are uncommon.

Ipratropium bromide

Efficacy: Several published trials have demonstrated that chronic therapy with ipratropium bromide improves FEV₁ in COPD patients (Level 1A). Reductions in resting and exercise dynamic hyperinflation have been demonstrated in patients who had little change in FEV₁ (14).

The optimal dosing of ipratropium bromide is not clear. Maximal bronchodilation may occur at doses greater than the recommended dose of 40 µg (two puffs) (15,16). Therefore, many clinicians recommend dosages of inhaled ipratropium bromide of 60 µg to 80 µg (three to four puffs), four times daily, for symptom control in COPD.

Dyspnea and exercise tolerance: Ipratropium bromide has also been shown to improve exercise tolerance and dyspnea in patients with COPD (Level 1A), during walk tests (4,5,8) and carefully standardized exercise tests (14).

Quality of life: It is unclear whether chronic use of ipratropium improves disease-specific quality of life (Level 1C) (17,18). The lack of clear improvement in quality of life measures despite effective bronchodilation has been observed with short-acting bronchodilators. Although these drugs offer effective bronchodilation, their effects are short lived and may not result in sustained improvements in hyperinflation and symptom relief.

Tiotropium bromide

Tiotropium is a long-acting anticholinergic bronchodilator which selectively binds and inhibits the M3 cholinergic receptor (19). The duration of action of tiotropium exceeds 24 h and the drug can thus be administered once daily at a dose of 18 µg/day. Tiotropium is an effective bronchodilator (Level 1A) and results in significant increases in FEV₁ (19). There is no decrease in the effects of tiotropium over 12 months of treatment (20).

Exercise tolerance: There is good evidence that tiotropium increases exercise tolerance and reduces associated dyspnea in COPD (21), probably by reducing hyperinflation.

Quality of life: Chronic use of tiotropium may improve disease-specific quality of life in COPD (Level 1B). Both dyspnea as

measured by the TDI and symptoms measured with the SGRQ improved more in tiotropium-treated patients compared with placebo-treated patients over 12 months (20).

COPD exacerbations and hospitalization rate: Tiotropium reduced the frequency of COPD exacerbations when compared with either placebo or ipratropium bromide (19,20). Compared with placebo (19), tiotropium reduced exacerbations from 0.95 to 0.76 per patient over one year ($P=0.045$). The mechanism for this reduction in exacerbations remains unclear. It may be that the sustained bronchodilation offered by tiotropium increases respiratory 'reserve' and that although exacerbations may still be occurring, the patient does not feel the need to seek medical attention.

Beta-2-adrenergic agonists

The principal action of the adrenergic agonists is to stimulate beta-2-adrenergic receptors on small airways, which increases cyclic adenosine monophosphate and relaxes airway smooth muscle with bronchodilation. Inhaled beta-agonists have a relatively rapid onset of action. The bronchodilating effects of short-acting beta-agonists usually wear off within 4 h to 6 h; however, long-acting beta-2-agonists (LABAs) are effective for 12 h or more, and do not show loss of effectiveness even with regular use in COPD (22-24).

Adverse effects of beta-2-agonists: Inhaled beta-2-agonists are generally well tolerated. Cardiovascular effects include tachycardia, palpitations and flushing. Extrasystoles and atrial fibrillation may also be seen. They may induce angina in patients with coronary artery disease. Central nervous system effects include irritability, sleeplessness and tremor. Other adverse effects of beta-2-agonists may include gastrointestinal upset, nausea, diarrhea, muscle cramps and hypokalemia (22,23). All of these side effects are uncommon when inhaled agents are used.

Short-acting beta-2-agonists (salbutamol)

Frequency of dosing for short-acting beta-agonists: Although commonly prescribed as regular (QID) therapy, there is little evidence that this regimen is better than the 'as needed' use of these drugs as rescue medications (25).

Exercise tolerance: Salbutamol, irrespective of method of administration or dose, improves exercise endurance as manifested by increased 6 min walk distances (Level 1A) (26,27).

Quality of life: It is unclear whether short-acting beta-agonists significantly improve quality of life in COPD (Level 1C). Conflicting results are available (28, 29).

LABAs (formoterol, salmeterol)

LABAs have a duration of action of at least 12 h (17,23,30,31). At present, there are two LABAs available in Canada: salmeterol and formoterol. Salmeterol has a delayed onset of action and a peak effect occurring over 1 h after administration, while formoterol has an onset of action within minutes, comparable with salbutamol.

Exercise tolerance: While there is little evidence that LABAs improve exercise performance as measured by walking distance (32), they do increase performance in standardized exercise testing (33).

Quality of life: LABAs have a beneficial effect in improving the patient's subjective sense of dyspnea (17,18) (Level 1B).

Several studies suggest that the regular use of LABAs also may result in an improvement in quality of life (18,34).

Methylxanthines

Theophylline causes bronchodilation, perhaps by increasing cyclic adenosine monophosphate due to inhibition of phosphodiesterase. Studies have shown that theophylline can increase lung function, decrease symptoms and enhance endurance during activities of daily living (35-39). Despite being an effective bronchodilator, theophylline's potential toxicities prevent it from being used as first line therapy. Adverse effects of theophylline include nausea, vomiting, insomnia, hyperactivity and tachycardia. Toxic levels can result in life threatening arrhythmias or seizures. Toxicity is dose-related and side effects are common, necessitating blood level monitoring. Many other drugs modify theophylline metabolism and care must be taken to monitor theophylline levels when new drugs such as macrolides or quinolones are added to a patient's therapeutic regimen.

Theophylline is also a ventilatory stimulant, so assessing its effect on exercise is complex.

Pulmonary function, dyspnea and quality of life measures: Murciano et al (35) noted a small but significant improvement in pulmonary function with theophylline and a more significant reduction in dyspnea, which may have been due to reduced hyperinflation. Improvements in dyspnea have also been observed during theophylline therapy (40).

Exercise capacity: It is unclear whether theophylline improves exercise capacity (Level 1C). Three studies found no significant effect on exercise endurance as assessed by a 12 min walk test (41-44). Some studies have found improvement on incremental exercise testing (44,45), while others have not (41-43).

Combinations of bronchodilators

Ipratropium and salbutamol: Combivent (Boehringer Ingelheim Pharmaceuticals, USA) is a combination product consisting of two bronchodilators, salbutamol and ipratropium. The combination is designed to benefit the patient by producing a greater bronchodilator effect than when either drug is used alone at its recommended dosage. There is evidence that this is the case (46-49).

Dyspnea, quality of life and exercise tolerance: There is no evidence available to suggest that the superior bronchodilating effects of Combivent translate into greater dyspnea relief or improved quality of life for patients with COPD, compared with that seen with ipratropium alone (28).

Ipratropium and LABA: Combinations of ipratropium bromide and LABA appear to produce improvements in pulmonary function over those seen with LABA alone, but little else in the way of benefit (50).

Theophylline and salmeterol: There appears to be no significant harm and possible benefit to the addition of a LABA to the regimen of patients who are already on treatment with (and tolerating) theophylline (50). With regard to patients on salmeterol, the small benefits of adding theophylline must be weighed against a significant potential for side effects.

Tiotropium versus LABA: There have been few head-to-head comparisons of tiotropium and LABA; further study is required before definitive conclusions can be drawn.

SUMMARY AND RECOMMENDATIONS

Bronchodilators are the most important agents in the symptomatic treatment of COPD. Bronchodilator therapy does not change the course of the disease.

1. Short-acting bronchodilators (both anticholinergics and beta-2-agonists) improve pulmonary function and exercise performance in COPD. They do not have a consistent impact on quality of life. Individual responses to the different classes are variable.
2. The use of short-acting anticholinergics and beta-2-agonists together produces superior bronchodilation than either drug alone (in conventional doses) and may be more convenient for some patients.
3. The long-acting anticholinergic, tiotropium, has been shown to have more sustained effects on pulmonary function, activity-related dyspnea and quality of life compared with ipratropium bromide. Tiotropium reduces exacerbation and perhaps hospitalization. Tiotropium is a once daily medication, and therefore compliance may also be improved with this preparation.
4. LABAs offer more sustained improvements in pulmonary function, chronic dyspnea and quality of life than short-acting bronchodilators. However, the effects of LABAs on exercise performance have been inconsistent.
5. While theophyllines are relatively weak bronchodilators, they offer modest improvements in pulmonary function, dyspnea and exercise performance. The addition of oral theophyllines to inhaled bronchodilator therapy may offer additive benefits in some patients.

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Recommendations (based on the published evidence):

1. For patients with relatively little disability, initiation of therapy with a short-acting beta-2-agonist as needed (or a regular anticholinergic or combination anticholinergic/beta-2-agonist) is acceptable. The choice of first line therapy in mild symptomatic COPD should be individualized and based on clinical response and tolerance of side effects (Level 1A).
2. For patients with persistent symptoms who are using short-acting bronchodilators more than twice per day, a long-acting bronchodilator should be considered. Recommended long-acting bronchodilators include the anticholinergic preparation, tiotropium (18 µg OD) or, alternatively, an LABA (formoterol 12 µg BID or salmeterol 50 µg BID) can be used (Level 1A). Short-acting beta-2-agonists can be used as needed for immediate symptom relief.
3. For patients with moderate to severe, persistent symptoms and exercise intolerance, a combination of tiotropium 18 µg OD and an LABA (ie, formoterol 12 µg BID or salmeterol 50 µg BID) may be of benefit, although it should be noted that this combination has not yet been specifically studied (Level 3). Short-acting beta-2-agonists can be used as needed for immediate symptom relief.
4. In patients with severe symptoms despite use of both tiotropium and LABA, a long acting preparation of oral theophylline may be tried, although monitoring of blood levels, side effects and potential drug interactions will be necessary (Level 3).
5. For patients who remain breathless and limited in their activity, despite combined long acting bronchodilation, a substitute for a LABA of an inhaled corticosteroid may be considered on an individualized basis.

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CORTICOSTEROIDS

Oral corticosteroids

Drug effectiveness: The most comprehensive study has been published by Callahan et al in 1991 (1) as a meta-analysis of 15 studies. They considered prednisone or methylprednisolone in doses of 30 mg or more daily for seven to 21 days. Analyses were restricted to FEV₁. An improvement of at least 20% of the FEV₁ from baseline occurred in about 10% of patients with stable COPD. Indicators such as the presence and extent of airway eosinophilia may be related to the degree of steroid-induced improvement of airflow obstruction (2-5). Withdrawal of oral steroids was not associated with any deterioration in patients given inhaled steroids (6).

Long-term effects of oral corticosteroids in stable COPD have been limited to observational studies (6,7) in mixed groups of patients.

Adverse effects: Systemic corticosteroids are known to cause a variety of serious adverse effects including adrenal suppression, osteoporosis, cataract formation, dermal thinning, muscle weakness, hypertension, diabetes, psychosis and hyperadrenocorticism (8-11). Due to risks in elderly patients with COPD, it would seem prudent to minimize the exposure to these agents.

Summary

Most patients with stable COPD do not benefit from systemic corticosteroids (1) and they carry significant risk. Although oral corticosteroids may be effective in an occasional patient with stable COPD, there are no reliable clinical parameters to identify those most likely to benefit. Only increased baseline eosinophil count in induced sputum has been shown to significantly correlate with reversibility of airflow obstruction following treatment with oral corticosteroids (2,3), and this is not an easy test to perform reliably.

RECOMMENDATIONS AND KEY MESSAGES

1. The limited benefit and the many adverse effects of oral corticosteroids in patients with stable COPD are important negative influences, and thus the clinician should generally avoid their chronic use (Level 1E).
2. Efforts should be made to try to wean patients who appear to be 'steroid-dependent' (Level 1B).

Inhaled corticosteroids

The use of inhaled corticosteroids in COPD is increasing (12-14), despite much weaker evidence of their benefits than in asthma. There is evidence that these drugs may be of some benefit, however.

Drug effectiveness

Effects on FEV₁: The short-term effects of inhaled corticosteroids on pulmonary function tests are variable, and the clinical meaning of a small initial improvement in FEV₁ in only a few studies is difficult to interpret.

More recently, four studies – the European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP) (15), the Copenhagen City Heart study (16), the Inhaled Steroids in Obstructive Lung Disease in Europe

(ISOLDE) (17) and the Lung Health II study (18) – have evaluated the effect of inhaled corticosteroids on long-term annual decline in FEV₁, and showed that inhaled corticosteroids did not slow the decline in lung function that characterizes COPD.

Effect on acute exacerbations: Several recent studies have assessed the effect of inhaled steroids on acute exacerbations. The bulk of the evidence indicates that inhaled steroid therapy reduces the frequency and/or severity of exacerbations in patients with relatively severe disease (FEV₁ less than 1.5 L) (17,19). Exacerbations apparently triggered by withdrawal of inhaled corticosteroids have also been observed (20,21).

A recent meta-analysis by Alsaeedi et al (22) demonstrated an overall reduction of COPD exacerbations of 30% (RR 0.70; 95% CI 0.58 to 0.84) in patients treated with inhaled corticosteroids. The results of this study with respect to exacerbation are presented in detail in Table 7.

This effect has been supported by two recently published large randomized clinical trials (23,24) designed to assess the effect of various treatments, including combination products, LABA, inhaled corticosteroids and placebo, on exacerbation. The data from the inhaled corticosteroids and placebo arms confirmed the beneficial effect of inhaled corticosteroids in reducing exacerbation in patients with moderate to severe COPD. Both showed a reduction in exacerbations with steroids on the order of 30% compared with placebo.

Effects on dyspnea and health status: Respiratory symptoms and health status have been examined in studies of inhaled corticosteroids in COPD, with mixed results. In mild disease, they have no effect (16,25). In moderate or severe disease, reductions in respiratory symptoms (18), rate of decline of health status and decreased withdrawal due to respiratory disease (26) have been noted. On the other hand, other large trials (23,24,27) have failed to confirm these benefits.

The results of these studies with respect to the effect of inhaled corticosteroids on respiratory symptoms and health status are somehow disappointing. It is possible but unproved that long-term treatment is needed to show an effect of inhaled corticosteroids on health status in COPD.

Effects on hospitalization and mortality: Several database studies have evaluated the effect of inhaled corticosteroids among COPD patients (28-32). Early studies found significant reductions in both mortality and hospitalizations in patients that have been previously hospitalized (28-30). These results contrast with those of more recent observational studies using different methodology (31,32), as well as results of randomized clinical trials (22); observational studies are much more susceptible to confounding and biases than randomized clinical trials (33). The benefits on hospitalizations and mortality attributed to inhaled corticosteroids in many database studies using similar methodology (28-30) could be explained in total or partially by numerous sources of bias that have not been identified or accounted for with proper analysis (32).

Factors predictive of a response to inhaled corticosteroids: Several potential markers of responsiveness have been tested including a personal or family history of asthma, seasonal or episodic dyspnea or wheezing, or atopy, but none have been shown to be reliably predictive of a response to inhaled corticosteroids in short-term trials. Responses to oral corticosteroids do not predict inhaled corticosteroid responses (17,34,35).

Adverse effects: Inhaled corticosteroids are well known to provide local reactions caused by their deposition in the oropharynx (36-38). Dysphonia has been reported to be the most frequent adverse effect (38), followed by oropharyngeal candidiasis and skin bruising (22).

Of greater clinical concern is the potential for systemic adverse effects, notably osteoporosis. There is conflicting evidence with regard to the effects of inhaled steroids on bone density (18), but increased fracture rates have not been documented (17). It is possible that the duration of follow-up has not been sufficient to determine differences in fracture rates attributable to inhaled corticosteroids.

An increased risk of cataract has been shown in observational studies in patients treated long-term with inhaled corticosteroids (39-41).

Summary

Clinical evidence is now accumulating to support therapeutic recommendations in particular clinical contexts. Large scale clinical studies have shown that inhaled corticosteroids have no influence on the long-term decline in lung function in COPD. Initial improvement in FEV₁ has been demonstrated in a few studies but the clinical significance of this acute effect is not established.

The main benefit of inhaled corticosteroids in COPD is a decrease in exacerbation rate. This is particularly true in more severe COPD (FEV₁ less than 1.5 L or 50% of predicted normal). It has also been demonstrated that exacerbations requiring oral corticosteroids can be prevented with regular inhaled corticosteroid therapy. This beneficial effect, which was first demonstrated with high dose inhaled corticosteroids (ie, fluticasone 1000 µg/day), has been recently observed with lower doses (ie, budesonide 800 µg/day).

Early database studies have reported that prescription of inhaled corticosteroids was associated with a reduction in mortality. This is in contrast with recent observational studies that have used a different methodology, as well as with randomized clinical trials that have not confirmed these findings.

Trying to decide which patient is likely to benefit from long-term treatment with inhaled corticosteroids still remains a challenge for the clinician. The best indication is the prevention of exacerbations in patients with severe disease.

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TABLE 7
Effect of inhaled corticosteroids on chronic obstructive pulmonary disease (COPD) exacerbation rates

Study	All COPD exacerbations (patient-months)		RR (95% CI)
	Treatment	Placebo	
Studies with systemic steroid run-in phase			
Vestbo et al (16)	155 (5220)	161 (5220)	0.96 (0.77 to 1.20)
Senderovitz et al (42)	NR	NR	NR
Bourbeau et al (43)	2 (225)	4 (210)	0.47 (0.09 to 2.52)
Burge et al (17)	1596 (8826)	2109 (7821)	0.67 (0.63 to 0.71)
Subtotal	1753 (14271)	2274 (13251)	0.77 (0.56 to 1.09)
Studies without systemic steroid run-in phase			
Lung Health II Study (18)	18 (22360)	39 (22280)	0.46 (0.26 to 0.80)
Renkema et al (44)	NR	NR	NR
Pauwels et al (15)	NR	NR	NR
Weir et al (45)	35 (816)	56 (828)	0.63 (0.42 to 0.96)
Paggiaro et al (19)	76 (852)	111 (834)	0.67 (0.51 to 0.88)
Subtotal	206 (23942)	206 (23942)	0.63 (0.51 to 0.77)
Total	1882 (387299)	2480 (37193)	0.70 (0.58 to 0.84)

Adapted from Alsaeedi et al (22). Not reported (NR) means not reported in the trial or not calculable from the available data. RR Relative risk

RECOMMENDATIONS AND KEY MESSAGES

1. Inhaled corticosteroids are beneficial in reducing exacerbations in patients with moderate to severe COPD (FEV₁ less than 1.5 L or 50% of predicted normal) and frequent exacerbations (Level 1A).
2. This beneficial effect, which was first shown with high doses of inhaled corticosteroids (fluticasone 1000 µg/day), has been recently observed with lower doses (budesonide 800 µg/day) (Level 1B).
3. Because inhaled corticosteroids do not slow the decline in lung function or reliably improve quality of life, the use of inhaled corticosteroids cannot be recommended as first line medication in COPD (Level 1E).
4. Trials of oral and/or inhaled corticosteroids do not predict the long-term benefit of inhaled corticosteroid treatment. Such trials are not recommended unless the patient is suspected to have underlying asthma (Level 1D).

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COMBINATION OF INHALED CORTICOSTEROIDS AND LONG ACTING BETA-2-AGONISTS PRODUCTS

Two combination inhaled steroid/LABA products are currently available in Canada: fluticasone/salmeterol and budesonide/formoterol.

To date, three published randomized controlled trials have investigated the combination of an LABA and an inhaled corticosteroid in COPD patients (1-3). Two of these studies (1,2) evaluated the 50/500 µg formulation of the salmeterol/fluticasone combination product and the third study (3) evaluated the 6/200 µg formulation of the formoterol/budesonide combination product. All three studies had a similar design: randomized patients to placebo, the combination, or one of the two components at the same dose as in the combination.

In these studies, the primary efficacy measure was FEV₁ although exacerbation was carefully evaluated in the Trial of Inhaled Steroids and Long-Acting Beta-2-Agonists (TRISTAN) (2) and Szafranski et al (3) studies. Patients included in these studies had COPD, a recent history of previous exacerbations, and mean FEV₁ of 1.0 L to 1.3 L.

Comparisons were made with the combination products and the placebo, LABA and inhaled corticosteroid arms. However, the real comparison of interest was that of the results seen with the combination products versus the results seen with the LABA component used alone. Another comparison was the impact on exacerbation of the combination products with the inhaled corticosteroid component used alone.

Lung function

In terms of FEV₁, the inhaled corticosteroid/LABA combination significantly improved lung function relative to placebo and to the inhaled corticosteroids arm, but not consistently relative to LABA. There was a small but statistically significant advantage (40 mL to 90 mL) to the combination in the TRISTAN study (2) but not in the Szafranski et al trial (3). The Mahler et al study (1) demonstrated that the combination product produced significantly greater improvements of trough FEV₁ than either drug alone (1), but this was not true of post-dose FEV₁.

Dyspnea

In all three studies, the inhaled corticosteroid/LABA combination significantly improved dyspnea and respiratory symptoms relative to placebo; however, there were no consistent effects on dyspnea seen when comparing the inhaled corticosteroid/LABA combinations with the LABA treatment component alone. Small differences favouring combination products were seen in the Mahler et al study (1) and in TRISTAN (2), but clinical significance is known only for the Mahler et al study (1), which used the TDI, a validated questionnaire. Dyspnea was similar in the combination and LABA groups in the Szafranski et al trial (3).

Health status

Health status was assessed in all three trials. In all three trials, the inhaled corticosteroid/LABA combination significantly improved disease-specific quality of life relative to placebo; it significantly improved disease-specific quality of life relative to inhaled corticosteroids only in the Mahler et al study (1). In TRISTAN (2), there were statistically significant but small differences between the combination product and salmeterol, favouring the former. The Szafranski et al trial (3) did not demonstrate statistically significant differences for symptoms between the combination product and LABA, or for inhaled steroids alone.

Exercise

Exercise tolerance was not reported in any of the three studies.

Exacerbations and hospitalizations

In all three studies, the inhaled corticosteroid/LABA combination significantly decreased the exacerbation rate and hospitalizations relative to placebo; however, exacerbation frequency was not changed relative to the inhaled corticosteroid treatment component alone, and only changed relative to the LABA group in the Szafranski et al study (3).

Summary

Preliminary information suggests that combined inhaled corticosteroid/LABA preparations may be superior to either drug alone in terms of improving pulmonary function. The mean improvement in FEV₁ with combination products compared with LABAs alone and inhaled corticosteroids alone are in the order of 40 mL to 75 mL, and 30 mL to 130 mL, respectively. The clinical significance of this small improvement in FEV₁ is difficult to interpret. Conversely, consistent improvements in dyspnea, quality of life and incidence of COPD exacerbation for combination products compared with LABAs have not been demonstrated. As well, there has not been any proof that the combination products can further reduce exacerbation compared with inhaled corticosteroids alone.

RECOMMENDATION

The clinical significance of the small improvements seen in FEV₁ for therapy with an inhaled corticosteroid/LABA combination product over the LABA component used alone in the therapeutic regimen for symptomatic COPD remains to be established. An inhaled corticosteroid/LABA combination should be reserved as a therapeutic trial for patients with persistent incapacity related to dyspnea despite optimal or maximal bronchodilator treatment (Level 3).

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PULMONARY REHABILITATION

Pulmonary rehabilitation was introduced to optimize COPD patients' functional status and overall autonomy (1). Subsequent research has confirmed its efficacy and established the scientific foundation of this intervention. A recent meta-analysis of 23 studies (2) concluded that pulmonary rehabilitation is effective in relieving dyspnea, enhancing exercise tolerance and improving quality of life (Figures 8,9).

It is important to appreciate that the magnitude of improvement in dyspnea, quality of life and exercise tolerance observed with rehabilitation is similar to what is usually obtained with pharmacological therapies, and thus, rehabilitation should be regarded as equally valuable. Therefore, a strategy incorporating both pharmacological and nonpharmacological approaches provides the greatest opportunity to optimize COPD (Figure 10).

Components of rehabilitation

Pulmonary rehabilitation comprises a variety of components, which can typically be grouped into three main categories: exercise training, patient teaching and self-management, and psychological support. It is often difficult to quantify the relative contribution of each specific component to the global improvement documented in these patients.

Exercise training: Because rehabilitation program results are similar to studies of exercise training alone, improvements in exercise performance and dyspnea can be attributed to the exercise component of the rehabilitation program (3) (Level 1A).

Lower extremity training: Evidence from several randomized controlled trials is available to support the use of a lower extremity exercise training regimen for patients with COPD (2) (Level 1A). Exercise training included walking (3-5), cycle ergometry (5-7) and treadmill walking (3,5,8). Subjects in the intervention groups showed significant increases in peak exercise capacity (3,5,7), timed walking distance (4,5,9) and submaximal endurance time (3,6).

There is also clear evidence of improvement in quality of life for COPD patients following lower limb exercise training (8-11). Furthermore, recent randomized controlled trials with long-term follow-up of patients documented a trend toward decreased hospital days (3,12), fewer exacerbations (13) and more efficient primary care use (12). Participation in a pulmonary rehabilitation program incorporating exercise training is associated with a trend toward reduced mortality rate compared with standard care alone (3,14).

Upper extremity training: Because training is specific to the muscle groups used, it is now recommended that upper extremity training be included in pulmonary rehabilitation (15) (Level 1B). Although such training improves arm strength and endurance (4,16), the impact of arm strength training on functional status and quality of life is not clear.

Strength training: Peripheral muscle weakness and wasting is common in COPD, the latter affecting up to 25% of all patients (17-20). Improving muscle mass and strength may be a reasonable therapeutic strategy in patients with COPD, but has not been well studied. Strength training improves peripheral muscle strength and endurance, submaximal exercise capacity and quality of life (9,21,22) (Level 1B), but it is not

clear whether the addition of strength training to aerobic training improves the outcome in terms of muscle function and exercise tolerance compared with aerobic training alone (23).

Education and self-management: Education and psychological support are thought to be important to the overall success of rehabilitation, but as noted, their specific roles are less well established. A recent study conducted in the province of Quebec evaluated the efficacy of a self-management program in patients with moderate to severe COPD (24). The program included standardized teaching supplemented by educational flipcharts and skill-oriented, self-help patient workbook modules. Patients were encouraged to increase their daily physical activities and to follow an exercise program. The main outcomes were quality of life and health care use in one year. The findings of the study were a marked reduction in use of health care services, and cost savings in the intervention group. The results suggest that integrating self-management strategies into the treatment of patients with COPD may be beneficial in terms of reducing health care use and associated costs (Level 1A).

Uncertainties and unproven interventions

It appears doubtful that inspiratory muscle training represents a useful addition to exercise training. In some studies, inspiratory muscle training improved exercise capacity compared with exercise training alone (25,26), while in other studies, it did not (27,28). A recent meta-analysis concluded that there was a tendency for further improvement in functional exercise capacity when inspiratory muscle training was used as an adjunct to general exercise training, but that this trend did not reach statistical significance (29) (Level 1C).

The addition of nutritional supplementation alone or in combination with anabolic medications to exercise training has been evaluated in a few studies (30-32) and was discussed in a meta-analysis (33). These interventions may produce increases in muscle mass compared with exercise training alone (30-32). However, the clinical relevance of this effect is questionable because the added benefit in terms of exercise tolerance is modest (Level 1C).

Cost effectiveness of pulmonary rehabilitation

The cost effectiveness of pulmonary rehabilitation added to standard care has been compared with that of standard care alone in three large, controlled, randomized clinical trials (34-36). The general conclusions of these studies were as follows: the extra expenses associated with pulmonary rehabilitation were completely offset by the reduction in health care use costs; the cost effectiveness profile was better for outpatient than inpatient pulmonary rehabilitation; and pulmonary rehabilitation was highly cost effective compared with many other interventions that are used in routine clinical practice. Considering the proven benefits, the time has come for pulmonary rehabilitation to be the standard of care in patients with COPD.

Inclusion criteria: Pulmonary rehabilitation should be considered in any COPD patient who remains symptomatic despite optimal bronchodilator therapy. Studies that have assessed the impact of exercise and rehabilitation have shown that the benefits occur irrespective of the subject's age (37), severity of

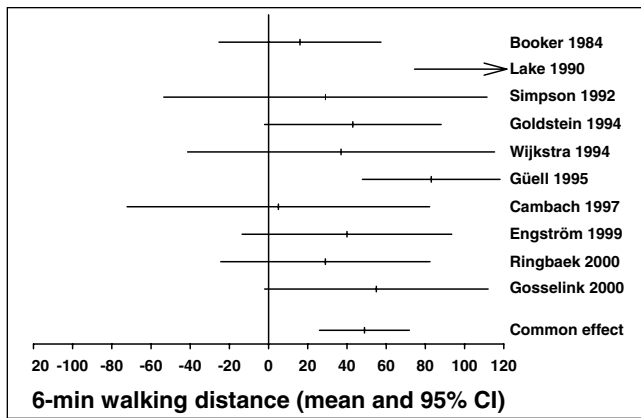


Figure 8) Effect of exercise training on functional exercise capacity (n=444). Adapted from reference 2

pulmonary impairment (38) or the presence of chronic respiratory failure, as evidenced by an elevated arterial carbon dioxide pressure (PaCO₂) (39). To minimize the predictable consequences of COPD, pulmonary rehabilitation should be used as early as possible in the natural evolution of the disease. **Exclusion criteria:** Pulmonary rehabilitation is safe in the vast majority of patients with COPD, even those with comorbid conditions such as coronary artery disease and hypertension, provided that the patient is adequately evaluated at the beginning of the program and that the exercise training regimen is adjusted according to the patient's health status. The initial evaluation should include a medical evaluation and baseline exercise testing. Because exercise is the principal component of pulmonary rehabilitation, the most common exclusion factor is the inability to exercise. External assessment of patient motivation should not be used as an exclusion criterion.

Long-term efficacy: Many of the benefits of exercise rehabilitation, particularly increased distance walked, decreased dyspnea with activity, and higher scores on quality of life measures, are sustained for several months to at least one year following the end of the exercise program (3,5,11-13,40). Because the initial improvement is progressively lost after stopping exercise, some sort of maintenance program is important. The components of such programs have varied.

Limitations of rehabilitation: Despite the many documented beneficial effects, pulmonary rehabilitation remains largely underused (41). Several factors may explain the apparent contrast between the efficacy of rehabilitation and the small number of patients undertaking this therapeutic modality. The limited availability of pulmonary rehabilitation programs is likely one of the most important factors. In 1999, there were only 36 pulmonary rehabilitation programs in Canada, with a capacity to accept no more than 4000 to 5000 patients with

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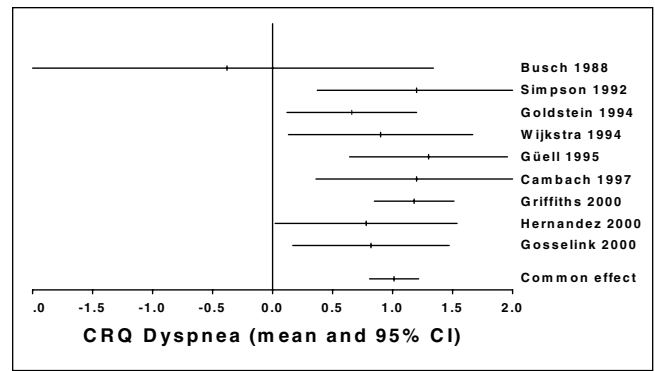


Figure 9) Effect of exercise training on dyspnea (n=519). Adapted from reference 2. CRQ Chronic Respiratory Disease Questionnaire

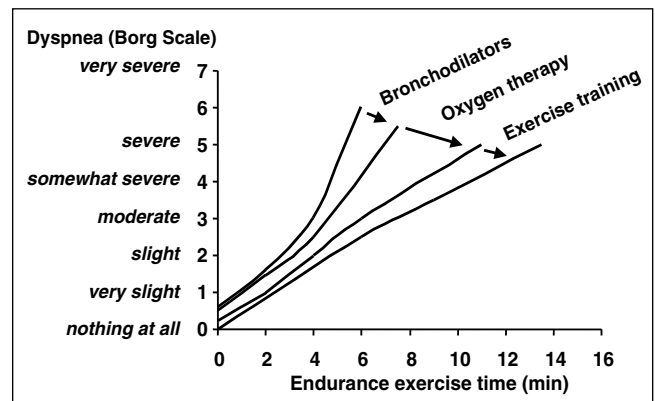


Figure 10) An approach combining optimal bronchodilation, oxygen therapy when indicated and exercise training will provide the greatest improvement in exercise tolerance. Adapted from reference 48

COPD per year, representing less than 1% of the COPD population (42). Part of the problem is that pulmonary rehabilitation in a hospital-based setting is not accessible to many patients with COPD. Strategies must be developed to improve availability of pulmonary rehabilitation at a lower cost. In this regard, self-monitored, home-based rehabilitation is a promising approach (43-47). However, only limited data are available on home-based rehabilitation and there is a need for further evaluation in a controlled trial.

KEY MESSAGE

COPD is a progressive, disabling condition that ultimately ends in respiratory failure and death. Physicians have a responsibility to provide support to COPD patients and their caregivers at the end of life.

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LONG-TERM OXYGEN THERAPY

Many countries have developed programs for domiciliary oxygen therapy in which supplemental oxygen is funded for use at home according to established criteria. However, there have been few well-designed, randomized controlled trials subsequent to the initial multicentre studies that established the life-saving benefits of oxygen. Most studies of chronic oxygen therapy have been in subjects with COPD, and it is commonly assumed that the data obtained from oxygen therapy in COPD can be applied to other hypoxemic states. Issues such as appropriate criteria for home oxygen, methods of evaluation of outcome, service delivery and follow-up remain either vague or completely absent from professional practice guidelines.

The role of supplemental oxygen must be placed within the context of a continuum of care, which should include cessation of smoking, maximal pharmacological therapy, appropriate vaccination, prompt attention to infectious exacerbations, and supervised programs in respiratory rehabilitation that aim to improve exercise tolerance and quality of life. Compliance with supplemental oxygen will be influenced by many psychosocial factors including the presence of a supportive family and an appropriate home environment. Patient and family education will assist in establishing realistic goals and expectations among all parties.

Survival and quality of life benefit

Knowledge base: Survival benefit of domiciliary oxygen has been documented by the Medical Research Council (MRC) and Nocturnal Oxygen Therapy Trial (NOTT) study group randomized controlled trials (1,2). Both studies were conducted in hypoxemic COPD patients (oxygen pressure [PaO_2] less than 60 mmHg), mostly males. The MRC study compared no oxygen with at least 15 h/day of domiciliary oxygen in the presence of cor pulmonale. The NOTT study compared continuous (24 h) with nocturnal (12 h) oxygen therapy. The continuous oxygen therapy group actually received oxygen for an average of 19 h/day. All patients received oxygen therapy during sleep. Both studies showed significant differences in all-cause mortality, favouring oxygen therapy. In the MRC study, survival improved in the oxygen therapy group after 500 days. In the NOTT trial, the 12 month mortality was 21% for nocturnal oxygen therapy and 12% for continuous oxygen use. Taken together, these trials demonstrated that the benefits from long-term oxygen therapy (LTOT) are dose-dependent: the longer the exposure to supplemental oxygen, the larger the benefits in terms of survival. Both studies were unblinded and neither addressed the influence of body mass index or smoking history on survival.

Quality of life was not quantitatively derived, although an improved sense of well being and improved neuropsychiatric function were reported.

A relatively recent, reasonably sized, unblinded randomized controlled trial (3) of domiciliary oxygen in COPD patients with mild hypoxemia (PaO_2 56 mmHg to 65 mmHg) failed to demonstrate a survival benefit. However, oxygen administration may have been suboptimal (13.5 h/day on average, without any increase in flow rate during sleep or activity). Two smaller randomized controlled trials did not document

increased survival in COPD patients with nocturnal desaturation and daytime PaO_2 levels above 60 mmHg (4,5).

Clinical implications: Current evidence (Level IA) supports the administration of domiciliary oxygen (more than 15 h/day to achieve SaO_2 greater than 90%) in stable COPD patients with severe hypoxemia (PaO_2 less than 55 mmHg) or when the PaO_2 is below 60 mmHg in the presence of cor pulmonale, right heart failure or erythrocytosis (hematocrit greater than 56%). These trials underpin the criteria for most programs in domiciliary oxygen. Unfortunately, the cost and ethics of randomizing subjects to a control group limit any chance of a repeat randomized controlled trial in which the control group receives room air.

Future studies: Large, well-designed studies would be necessary to address quality of life issues in the above population. These will likely come from observational studies and case series, with or without control subjects. Studies to examine the potential survival benefits of domiciliary oxygen in COPD patients with milder degrees of hypoxemia (5,6) remain of interest.

Sleep

Knowledge base: It has been suggested that nocturnal oxygen desaturation (NOD) in COPD increases mortality (4). NOD has also been associated with poor sleep quality as indicated by reduced sleep time, increased sleep stage changes and increased arousal frequency (7). Nocturnal oxygen therapy has not been shown to increase survival in COPD patients with 'isolated' NOD, nor was it consistently effective in improving sleep quality in these patients (8,9). Because obstructive sleep apnea is common, there is a high likelihood that a few patients will have both conditions.

Clinical implications: Existing evidence does not support the prescription of nocturnal oxygen therapy for COPD patients with (isolated) nocturnal desaturation. Obstructive sleep apnea and chronic hypercapnic respiratory failure should be separated from COPD because they represent different diagnostic categories with alternative approaches to management. However, clinical management of transient sleep desaturation sometimes includes nocturnal oxygen therapy if desaturation occurs for protracted periods (eg, more than 30% of the time in bed at an SaO_2 less than 88%) or in the presence of pulmonary hypertension, cor pulmonale or other associated medical conditions that might influence survival.

Organizational implications: Funding criteria for nocturnal oxygen therapy varies between program jurisdictions, with some programs requiring a physician's letter documenting the evidence for nocturnal desaturation and making the clinical case for funding. Oximetry alone will suffice for most patients. Full polysomnographic measurements should be reserved for those suspected of having sleep apnea by history or by the characteristic oscillating pattern on the oximeter trace.

Future studies: The management of transient nocturnal desaturation remains unclear and requires further clinical trials.

Exercise and dyspnea

Knowledge base: Moderate hyperoxia (fraction of inspired oxygen 0.4 to 0.6, which achieves a PaO_2 greater than 200 mmHg) during submaximal exercise testing increases

exercise time, reduces exercise minute ventilation and may delay respiratory muscle dysfunction in patients with moderate to severe COPD. Improved exercise performance is correlated with decreased lactate production (10-12). Supplemental oxygen administered via nasal cannulae diminishes transient exercise hypoxemia and has been associated with modest (10%), variable improvements in exercise capacity, as well as improved dyspnea scores (13-15). In randomized controlled trials in which subjects underwent supervised exercise rehabilitation with oxygen or air, this transient improvement did not result in a significant difference in exercise tolerance, dyspnea scores or HRQoL between groups (16-17).

Although COPD patients with the most exercise desaturation tend to show the greatest benefit from oxygen supplementation, this observation does not enable clinicians to predict individual responses. Significant (greater than 10%) improvements in exercise capacity and dyspnea scores (greater than two) occurred in some desaturators (four of 11 in a recent study [15]) but are occasionally observed among nondesaturating patients.

Clinical implications: Prescription of ambulatory oxygen for COPD patients with resting normoxia (SaO_2 greater than 88%) but transient exercise desaturation should be limited to individuals with a documented (blinded and repeatable) acute improvement in dyspnea and exercise performance with oxygen. To date, there is insufficient evidence to justify more widespread prescriptions for all ambulatory COPD patients with transient desaturation or profound dyspnea on activity.

Organizational implications: This is an area for clarification. Subjective identification as to whether oxygen provided an important clinical benefit resulted in indistinguishable answers between patients who were eligible for oxygen funding and those who were not (18). In both groups, 80% of respondents identified oxygen as providing an important benefit.

Future directions: Studies are required to better define who might benefit from oxygen during transient exercise desaturation. The outcomes are unlikely to relate to living longer and therefore such studies should focus on improvements in HRQoL (living better).

Ambulatory oxygen

Knowledge base: In patients with resting hypoxemia, LTOT provided by a stationary system may limit the ability of patients to remain active by encouraging psychological dependence and fear of leaving home. Combined domiciliary and ambulatory oxygen has been proposed as a solution to this issue (19,20). Only one randomized trial (21) has addressed the issue of the effect of portable oxygen in COPD patients who also meet the criteria for LTOT. In this 12-month trial, 159 patients were randomly provided with oxygen concentrators ($n=75$) or concentrators plus portable oxygen, either by cylinder ($n=51$) or by liquid ($n=33$) system. Those with portable systems used more oxygen than those without (17 h versus 14 h), although 40% did not use the oxygen adequately. Patients who used oxygen for more than 18 h/day (including many in the portable group) self-reported more outside activities than those who used oxygen for less than 15 h/day.

Clinical implications: Although portable oxygen delivery systems are currently available, they are expensive and no study

has firmly demonstrated their effectiveness in improving patient-oriented clinical outcomes. Ambulatory oxygen might increase compliance with oxygen by increasing the daily dose (21). It might also increase mobility, exercise tolerance, confidence and autonomy (22,23), although the potential for a placebo effect is very high. Therefore, careful patient selection, formal assessments and subsequent supervision are recommended (24).

Organizational implications: Consensus conferences (25) on domiciliary oxygen therapy have consistently recommended ambulatory oxygen for those patients with resting hypoxemia who are mobile. In the absence of evidence of effectiveness, this is clearly an area for further study. Initial supervision is important to ensure that portable oxygen is being used to enhance mobility. Patient education regarding the goals of ambulatory oxygen is important.

Future directions: The use of ambulatory oxygen in conjunction with home oxygen warrants further evaluation before its routine clinical use in patients with COPD can be recommended.

Oxygen for air travel

Knowledge base: Small studies and expert reviews (Level 3) (26) form the basis of the following information. In addition to the stress of airline travel and the immobility associated with sitting for many hours, COPD patients experience altitude hypoxemia, which has the potential to increase morbidity. Newer aircrafts pressurize their cabins to a lower altitude than older aircrafts (27). Respiratory incidents are rare and account for only a small percentage of serious events (28). Patients with a resting PaO_2 of less than 70 mmHg will have inflight PaO_2 levels of 50 mmHg to 55 mmHg.

Clinical implications: Physicians may be asked to identify and advise patients at risk for problems during air travel. These include patients with COPD, especially if they have hypoxia, hypercapnia, recent exacerbations or a history of difficulty in flight. Some physicians may prefer to send their patients to established assessment centres.

Organizational implications: Issues of physician responsibility should be separated from patient and airline responsibility for health during air travel.

Future directions: Prospective trials are needed to establish the true incidence of complications among patients with COPD. A coherent national policy regarding the use of oxygen in aircraft would be helpful.

Adverse events

Safety: Supplemental oxygen administered to patients with COPD who are clinically stable results in only minimal (less than 5 mmHg) increases in carbon dioxide tension during the day, with no evidence of further increases at night (29).

The prescription of LTOT for smokers remains inconsistent despite the physiological evidence that carboxyhemoglobin inhibits the effect of supplemental oxygen (30), as well as the obvious fire hazard of combining smoking and oxygen. This is an area in which clinical decisions are made by physicians on an individual basis.

Clinical implications: Although there are few formal studies, prescribing domiciliary oxygen for patients who continue to smoke is questionable from physiological and psychological points of view (lack of commitment to wellness).

Organizational implications: Applications for funding domiciliary oxygen for patients who continue to smoke should be carefully reviewed. Patients who smoke should be directed to credible smoking cessation programs.

Future directions: Smoking cessation must be part of the comprehensive care provided to patients with chronic respiratory conditions.

Assessment and reassessment

Knowledge base: There is very limited information on the optimal approach to assessment and reassessment of domiciliary oxygen therapy. Practices vary between the various jurisdictions. Clinical stability is essential because many patients who appear to meet criteria for LTOT do not meet these criteria when they become clinically stable (31). Reassessment is valuable in demonstrating (or not demonstrating) continuing stability.

Clinical implications: Current procedures for administration and reimbursement of home oxygen may result in some recipients not meeting the criteria. For those who do, the prescription of oxygen flow rates needs to match their requirements.

Organizational implications: Oxygen assessors should be independent of oxygen providers. Standardized national criteria for administration of LTOT should be developed. These should include criteria for assessing, prescribing and monitoring patient compliance. To ensure that the patients are stable, a confirmatory three-month assessment is recommended, provided the patient has not experienced a recent exacerbation (hospitalization or a change in therapy). Subsequent annual assessments may not be necessary if the initial and confirmatory assessments reflect the need for LTOT in a stable patient.

Future directions: Shared provincial experiences, consensus guidelines and program evaluations all have the potential for more effective resource allocation in LTOT.

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Summary

In clinically stable patients with COPD and resting hypoxemia, evidence that LTOT is life-saving has resulted in the widespread use of domiciliary oxygen therapy. Conclusions from the only two large, randomized, multicentre trials have been applied to a variety of other circumstances and diagnostic categories, perhaps resulting in clinical practice extending beyond the scientific basis of effectiveness. Many outstanding clinical and service delivery issues remain. They include: LTOT for transient hypoxemia associated with exercise or sleep, indications for ambulatory oxygen therapy, when to re-evaluate those receiving LTOT, whether to prescribe LTOT for those who continue to smoke, and how to write an oxygen prescription. Multicentre collaborative studies would be the most effective approach to addressing these issues. Coherent national policies on LTOT might reduce disparities among jurisdictions and provide opportunities for appropriate resource use.

KEY MESSAGES

- LTOT is life prolonging for stable COPD patients with resting hypoxemia (Level 1A).
- There is little evidence to support prescribing LTOT during transient sleep or exercise-induced hypoxemia, or for dyspnea.
- There are many outstanding issues regarding the indications, prescription, equipment and timing of the clinical evaluation for patients receiving LTOT.
- The role of LTOT for smokers remains controversial.
- Coherent national policies would reduce regional disparities in the provision of LTOT and provide opportunities, through program evaluation, for improved resource allocation.

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ACUTE EXACERBATIONS OF COPD

Acute exacerbations are the most frequent cause of medical visits, hospital admissions and death among patients with COPD (1). In addition, frequent exacerbations are an important determinant of quality of life measures (2) and contribute to accelerated rates of decline in lung function (3). There are no characteristic laboratory, roentgenographic or physiological tests to establish a diagnosis of acute exacerbations of COPD (AECOPD); clinical definitions are used and data regarding AECOPD may depend on the definition used.

Definitions

Anthonisen et al (4) proposed three clinical criteria to define AECOPD: increased sputum volume, increased sputum purulence and increased dyspnea. The most severe, or type I, exacerbation includes all three of these symptoms. A type II exacerbation exhibits any two symptoms. A type III exacerbation exhibits one symptom plus at least one of the following: an upper respiratory tract infection in the past five days, increased wheezing, increased cough, fever without an obvious source or a 20% increase in respiratory rate or heart rate above baseline (4). Seemungal et al (5) have also proposed the use of major and minor criteria to define an exacerbation. The major criteria are the three proposed by Anthonisen. Minor criteria include wheezing, sore throat, or symptoms of a common cold such as nasal discharge or congestion. The authors define an exacerbation as the presence of at least two major symptoms or one major and one minor symptom for at least two consecutive days. Using these definitions, the average COPD patient experiences two to three exacerbations per year (2,5,6). Frequency of exacerbations is, in part, related to severity of underlying airflow obstruction (6-8), and patients with a previous history of frequent exacerbations are more likely to have frequent exacerbations in the future (9,10). Patients with chronic dyspnea and poor lung function may worsen symptomatically to the point of needing medical care or hospitalization without necessarily meeting most current definitions for AECOPD.

The authors propose that AECOPD be defined as a sustained worsening of dyspnea, cough or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications. The term 'sustained' is included in the definition to separate an AECOPD from the normal day-to-day variations in COPD symptoms. In addition, AECOPD can be subclassified as either purulent or nonpurulent; this is helpful in predicting the need for antibiotic therapy.

Clinical consequences of AECOPD

AECOPD may lead to hospitalization, which is associated with variable mortality depending on the severity of the underlying COPD. Patients with mild to moderate disease have a 4% short-term mortality if admitted to hospital (11), but mortality rates can be as high as 24% if patients are admitted to an intensive care unit (ICU) with acute respiratory failure (12-15). In addition, patients requiring ICU admission have a one-year mortality rate as high as 46% (12,13,15). A significant percentage of patients requiring hospitalization for AECOPD will require subsequent readmissions because of persistent symptoms (12,16-18).

Diagnostic evaluation

The etiology of AECOPD is often difficult to determine. At least one-half of all exacerbations are thought to be infectious in nature; many of these are viral in origin, while the remainder is due to bacterial infection. Other noninfectious triggering factors for exacerbations include exposure to allergens, irritants (cigarette smoke, dust), cold air (19) or pollutants (20-22).

There are no diagnostic tests that define AECOPD. A complete history and physical examination should be performed to rule out other causes for worsening cough and dyspnea. Patients who are very dyspneic should have a measurement of arterial SaO₂ and consideration should be given to performing an arterial blood gas test.

In outpatient assessments of patients, chest roentgenograms should be considered if there is a possibility of pneumonia, congestive heart failure or pneumothorax. Chest roentgenograms are recommended for all patients presenting to an emergency room or hospitalized with AECOPD, because they have been shown to reveal abnormalities that lead to a change in management in 16% to 21% of patients (23-25).

Sputum Gram stain and culture have not been shown to be helpful. However, they should be considered for patients with poor lung function, frequent exacerbations (more than three per year) or who have been on antibiotics in the preceding three months.

While it is important to know the level of lung function in stable COPD patients, there is little evidence to suggest that spirometry should be performed during AECOPD. There appears to be a poor correlation between transient falls in lung function and the severity of the exacerbation, at least as measured by symptoms (5). The development of an acute exacerbation of COPD should be a motivating factor to obtain objective measurements of pulmonary function following recovery in individuals who have not previously had spirometry.

Treatment of AECOPD

Bronchodilators: Much of the literature exploring the role of inhaled bronchodilator therapy in patients with AECOPD has been carried out in emergency rooms or hospital. Substantial evidence has accumulated to show that all inhaled bronchodilators can improve FEV₁ during an AECOPD, and studies of bronchodilators have been confined to comparing different agents.

A number of studies have compared inhaled ipratropium to short-acting beta-agonists (26-30). They showed that results were essentially the same for the two agents and that combining them did not produce more improvement than the use of single agents. There is no advantage to systemic administration of beta-agonists.

There have been controlled trials comparing metered dose inhalers (MDIs) to nebulized bronchodilators, and the preponderance of the evidence indicates that MDIs were as effective as wet nebulizers in improving lung function (31-35).

The benefit of adding intravenous aminophylline to inhaled bronchodilators has been examined in two randomized trials in COPD patients (36,37), and did not result in improved pulmonary function, reduced symptoms or decreased relapse rates requiring emergency room visits. The addition of

aminophylline was associated with an increased risk of adverse effects, specifically nausea and vomiting (38).

Inhaled bronchodilators should be used to treat patients with AECOPD. Because some patients benefit from combination therapy, this is recommended in the acute situation. Due to the lower cost of using MDIs with a spacer, this route would be preferred over wet nebulization in most situations. There is no clear role for initiation of therapy with theophyllines during an AECOPD, but in patients who are already on an oral methylxanthine product, it is reasonable to continue the medication, provided drug interactions are considered and theophylline levels monitored.

Corticosteroid therapy: Systemic corticosteroids are of benefit in AECOPD, in terms of more rapid recovery of FEV₁, more rapid improvement in recovery of PaO₂, decreased treatment failures and shorter hospitalization rates in emergency room studies (39-43).

There are a number of limitations to the current trials examining the role for systemic corticosteroid therapy in AECOPD. All but one of the trials (41) were performed in emergency room or hospital ward settings. The dose and duration of corticosteroid therapy varied widely between studies, making it rather difficult to provide specific treatment recommendations. There appears to be no benefit to treating for longer than two weeks (43), and 10 days of therapy appears to be more effective than three days (44).

One trial (45) examined the use of high dose inhaled corticosteroids in AECOPD. Nebulized budesonide (2 mg every 6 h for a total of 72 h) was as effective as prednisolone (30 mg twice daily for a total of 72 h) and both were better than placebo in terms of recovery of FEV₁. Whether similar beneficial effects could be demonstrated with lower doses of inhaled corticosteroids remains to be determined.

There is good evidence to support the use of oral or parenteral corticosteroids in moderate to severe AECOPD. The exact dose and duration of therapy should be individualized, but 25 mg/day to 50 mg/day of prednisone or the equivalent for treatment periods of between seven to 14 days seem reasonable. The role for oral corticosteroid therapy in outpatients with milder AECOPD remains unclear. The role of high dose inhaled corticosteroid therapy during an AECOPD warrants further investigation.

Antibiotics: Although at least one-half of all exacerbations are felt to be infectious in origin, there are no diagnostic tests to reliably confirm the presence of a bacterial infection. Complicating this problem is the fact that many COPD patients have chronic lower airway colonization with potentially pathogenic bacteria. Anthonisen et al (4) were the first to suggest a severity index to predict the benefit of antibiotic therapy. Patients with a type I exacerbation (with increased sputum volume, purulence and dyspnea) had the worst outcomes on placebo and demonstrated the largest benefits from antibiotic therapy. For those patients with a type II exacerbation (two of the cardinal symptoms), the benefit was less apparent. There was no clinically relevant difference between antibiotic- and placebo-treated groups in patients with type III exacerbation (one of the cardinal symptoms, usually dyspnea). Stockley et al (46) demonstrated that the presence of green (purulent) secretions in dyspneic

COPD patients indicates a high bacterial load and may identify a subset of patients who will benefit from antibiotic therapy.

A 1996 meta-analysis (47) of randomized controlled trials of antibiotic therapy concluded that antibiotics led to a small but statistically significant improvement in AECOPD outcomes. Peak expiratory flow rates demonstrated a mean increase of 10.75 L/min in favour of the antibiotic-treated group.

Based on the preceding studies, it is recommended that patients with more severe exacerbations (eg, types I or II as determined by the Anthonisen criteria) are likely to experience greater benefit from antibiotics.

The question of which antibiotic to use is an issue. Many organisms implicated in AECOPD are resistant to the antibiotics used in previous clinical trials, but there are few good head-to-head comparisons of different agents. It has become popular to stratify patients based on their risk of treatment failure and to choose antibiotic therapy based on their risk category (48). These stratification schemes have not been validated in a prospective fashion.

Patients with purulent exacerbations should be divided into two groups – simple or complicated exacerbations – based on the presence of risk factors that either increase the likelihood of treatment failure or have an enhanced association with more virulent or resistant bacterial pathogens (Table 8). Patients with simple AECOPD have no risk factors for treatment failure and antibiotic therapy should be targeted against the most likely pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*). In the absence of reports of clinical failures caused by antibiotic resistance in this group of patients, relatively inexpensive antibiotics are recommended for this group. These include aminopenicillins, doxycycline and trimethoprim/sulfamethoxazole.

Patients with complicated AECOPD have risk factors that are associated with an increased likelihood of treatment failure or infection with a more virulent or resistant organism (Table 8). As a result, antibiotics with enhanced antimicrobial coverage are recommended. No head-to-head comparisons powered to show a benefit of one class of antibiotics over another in terms of clinical outcomes have been done. There are suggestions that fluoroquinolones may be the best current choice in AECOPD with multiple risk factors or frequent exacerbations (49-52).

Patients treated with antibiotics appear to have an increased risk of developing resistance to the same class of antibiotics within a finite time interval. Therefore, if a patient requires repeat antibiotic therapy within three months, a new class of antibiotics should be used. Table 8 summarizes antibiotic treatment recommendations for patients with purulent AECOPD.

Prevention of AECOPD

Given the costs and consequences attributable to AECOPD, any therapy that reduces the frequency of these exacerbations would be welcomed. Several preventive strategies are covered elsewhere in this document and will be mentioned briefly.

Smoking cessation reduces the rate of lung function decline, confers a survival advantage and leads to symptomatic improvement in COPD patients. It also reduces the number of respiratory infections.

TABLE 8
Antibiotic treatment recommendations for purulent acute exacerbation chronic obstructive pulmonary disease (COPD)

Group	Basic clinical state	Symptoms and risk factors	Most likely pathogens	First choice antibiotic	Alternative antibiotics
Simple	COPD without risk factors	Increased cough and sputum, sputum purulence and increased dyspnea	<i>Haemophilus influenzae</i> , <i>Haemophilus</i> spp, <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i>	Amoxicillin, doxycycline, trimethoprim/sulpha- methoxazole, 2nd or 3rd generation cephalosporins, extended spectrum macrolides	Beta-lactam/ beta-lactamase inhibitor Fluoroquinolone
Complicated	COPD with risk factors	Same as for simple, plus at least one of the following: • FEV ₁ <50% predicted • ≥ four exacerbations/year • Ischemic heart disease • Use of home oxygen • Chronic oral steroid use • Antibiotic use in the past three months	Same as for class I, plus • <i>Klebsiella</i> spp and other Gram-negative spp • Increased probability of beta-lactam resistance	Beta-lactam/ beta-lactamase inhibitor Fluoroquinolone Antibiotics for uncomplicated patients, when combined with oral steroids, may suffice	May require paren- teral therapy Consider referral to a specialist or hospital

COPD patients infected with influenza have a significant risk of requiring hospitalization. An annual influenza vaccination reduces morbidity and mortality from the disease by as much as 50% in the elderly and reduces the incidence of hospitalization by as much as 39% in patients with chronic respiratory conditions (53,54). Annual influenza vaccination is recommended for all COPD patients who do not have a contraindication.

The benefit of pneumococcal vaccine in COPD is less well established. Some reports state that the vaccine has up to a 65% efficacy in COPD patients (55), although an effect on reducing the frequency of AECOPD has yet to be established. The authors recommend that all patients with COPD be given pneumococcal vaccination at least once in their lives and that consideration be given to repeating the vaccine in five to 10 years in high risk patients.

Various oral immunostimulating agents, targeted either against *H influenzae* alone (56) or multiple bacterial pathogens (57), have been shown to decrease the frequency of AECOPD, the need for antibiotic usage, and hospitalization rates due to COPD. If available in Canada in the future, annual use of an immunostimulating agent would be recommended.

Chronic therapy with inhaled corticosteroids does not slow down the rate of decline in FEV₁, but does appear to reduce the frequency of AECOPD in prospective trials (7,8). The authors recommend that patients with frequent AECOPD (more than three episodes per year) should be considered for treatment with inhaled corticosteroids.

There is some preliminary evidence to suggest that COPD patients treated with LABAs or tiotropium, a long acting anticholinergic agent, have a delayed time to their next exacerbation compared with patients receiving placebo or ipratropium bromide (58-60). It is unclear whether these effects are additive between different classes of long acting bronchodilators or to that achieved with inhaled corticosteroids alone (61). Further investigations will be necessary before LABAs, long acting anticholinergics or combination products can be routinely recommended for this purpose.

Currently, there is no evidence to support the use of prophylactic antibiotics in the prevention of AECOPD.

Summary

1. AECOPD is defined as a sustained worsening of dyspnea, cough or sputum production, leading to an increase in the use of maintenance medications or supplementation with additional medications (Level 3).
2. AECOPD should be subclassified as either purulent or nonpurulent, to help predict the need for antibiotic therapy (Level 2A).
3. Arterial SaO₂, with consideration given to performing an arterial blood gas, is recommended for all patients who present to an emergency room or who are hospitalized with AECOPD (Level 3).
4. Chest roentgenograms are recommended for all patients who present to an emergency room or who are hospitalized with AECOPD (Level 2).
5. Sputum Gram stain and culture should be considered for patients with poor lung function, frequent exacerbations (more than three episodes per year) or who have been on antibiotics in the preceding three months (Level 3).
6. It is not recommended that spirometry be performed during an actual AECOPD except for diagnostic purposes in a patient without a known history of COPD (Level 3).
7. Inhaled bronchodilators should be used to treat all patients with AECOPD (Level 2A).
8. Combination short-acting bronchodilator (ie, beta-agonist and anticholinergic) therapy is recommended in the acute situation (Level 3).
9. An MDI with a spacer is the preferred delivery device for inhaled bronchodilators in most situations (Level 1B).
10. There is no role for initiation of therapy with a theophylline medication during AECOPD (Level 1E). For patients who are already on an oral theophylline, it is reasonable to continue the medication during an AECOPD, with monitoring of drug levels (Level 3C).
11. There is good evidence to support the use of oral or parenteral corticosteroids during AECOPD in patients with severe airflow obstruction (eg, FEV₁ less than 50% predicted) (Level 1A). The exact dose (25 mg/day to

- 50 mg/day of prednisone or equivalent is suggested) and duration (seven to 14 days is reasonable) of therapy should be individualized (Level 2B).
12. Antibiotics are beneficial in the treatment of severe AECOPD based on Anthonisen criteria (ie, more than two of the following criteria: increased dyspnea, increased sputum volume and change in sputum purulence from baseline) (Level 1A).
 13. AECOPD should be subdivided into two groups – simple or complicated – based on the presence of risk factors that increase the likelihood of treatment failure or that have an enhanced association with more virulent or resistant pathogens (Level 2B). Antibiotic choice is guided by this classification scheme of AECOPD (Level 2B).
 14. If a patient requires repeat antibiotic therapy within three months for AECOPD, a new class of antibiotics should be used (Level 2B).
 15. Annual influenza vaccination is recommended for all COPD patients who do not have a contraindication (Level 2A).
 16. Pneumococcal vaccination should be given to all COPD patients at least once in their lives; in high risk patients, consideration should be given to repeating the vaccine in five to 10 years (Level 3C).
 17. If available in Canada in the future, annual use of an immunostimulating agent would be recommended (Level 2A).
 18. Patients with frequent AECOPD (more than three episodes per year) should be considered for treatment with inhaled corticosteroids (Level 2A).
 19. Further studies are necessary to determine the role of long acting bronchodilators or combination products (ie, inhaled corticosteroids plus long acting bronchodilators) in the prevention of AECOPD (Level 3B).

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CLINICAL PRACTICE GUIDELINES FOR NONINVASIVE MECHANICAL VENTILATION IN COPD

Introduction

Mechanical ventilation: Some patients with an AECOPD develop such severe respiratory distress that ventilatory support is required to ensure short term survival. Conventional mechanical ventilation, including the placement of an endotracheal tube, was the only option until the 1990s.

Noninvasive ventilation: Numerous randomized controlled trials and a recent systematic review (1-9) support the benefit of noninvasive positive pressure ventilation (NPPV) in the setting of acute exacerbations. NPPV should be strongly considered in AECOPD with associated respiratory failure (as indicated by persistent respiratory acidosis) despite initial therapy with bronchodilators (pH less than 7.30) (Level 1A). There is also a strong suggestion that the use of noninvasive ventilation in this setting is cost effective (10) (Level 2A).

Not all patients with COPD exacerbations benefit from NPPV (see Table 9). The lower the pH (especially when the pH less than 7.25) and higher the PaCO₂ at presentation, the less likely patients are to respond (11). Patients treated with NPPV who do not improve within the first 4 h are unlikely to benefit from NPPV (11,12). These patient groups should be closely monitored because they have a higher likelihood of requiring conventional mechanical ventilation (Level 2B). Conversely, patients with normal or mildly reduced pH (greater than 7.30), who are not severely dyspneic, also do not seem to clearly benefit from the addition of NPPV (5,9) (Level 1B).

A large randomized controlled trial (8) on the use of NPPV in patients with AECOPD treated on a respiratory ward rather than the ICU reported a reduction in mortality for the group treated with NPPV for patients with severe (pH less than 7.30) and less severe exacerbations. However, the mortality rate of the severe subgroup of patients treated on the ward with NPPV was higher than that reported in the literature for apparently similar patients treated in the ICU. In patients with severe COPD exacerbations, NPPV should be initiated in a setting that provides adequate cardiopulmonary monitoring (Level 2B).

A combined nasal/oral (or full face) mask is preferable, but nasal mask alone has been used in this setting (Level 3B). Pressure support has been demonstrated to be more comfortable than assist control (13) (Level 1B), and this may be provided by a conventional ventilator or a ventilator developed specifically for noninvasive ventilation. Proportional assist ventilation may be more comfortable than pressure support but more study is required (14,15) (Level 1B). Helium-oxygen mixtures with NPPV reduce the work of breathing in patients with AECOPD (16,17) (Level 1C), but the patients studied were quite stable; helium has yet to be studied in more acute, severe exacerbation.

The use of NPPV in hypercapnic patients with stable COPD has not demonstrated any consistent clinically or statistically significant impact on outcome (18) and therefore cannot be recommended at this time (Level 1E).

Invasive ventilation: The goals of mechanical ventilation in COPD patients are rest of fatigued respiratory muscles, ventilatory support during treatment of reversible conditions, and correction of severe hypoxemia and/or hypercarbia. Assist

control ventilation provides more respiratory muscle rest and reduced work of breathing than synchronized intermittent mandatory ventilation (19). Pressure control ventilation reduces the risk of barotrauma, and may improve patient-ventilator synchrony (20) and reduce the work of breathing (21) compared with volume cycled ventilation (Level 2B). The goal is to prevent dynamic hyperinflation; settings depend on adequate sedation of patients to prevent suddenly high respiratory rates.

The application of external positive end expiratory pressure (PEEP_e) in patients with elevated internal PEEP (PEEP_i) may reduce the effort required to trigger the ventilator, work of breathing, flow resistance and PEEP_i (22-27). In patients with high levels of PEEP_i in spite of sedation, paralysis and efforts to achieve maximal bronchodilation, the addition of helium and oxygen in a ratio of 70 to 30 may be useful (28) (Level 2B).

Weaning studies comparing T-piece and pressure support ventilation (PSV) suggest that both produce similar weaning times (29,30), and both are more effective than synchronized intermittent mandatory ventilation (Level 1B). The only trial (31) comparing T-piece trials to PSV in COPD patients found no difference in outcome. Daily spontaneous breathing trials (32) and weaning protocols (33-35) have been shown to reduce the duration of weaning in ventilated ICU patients (Level 1B). While one study (36) strongly suggested that early extubation to noninvasive ventilation results in both a reduction in length of stay and hospital mortality, a second study (37) (which included non-COPD patients) did not achieve the same results. Early extubation to noninvasive ventilation in a closely monitored environment may be beneficial for COPD patients, but further work is required in this area (Level 1B).

COPD patients who develop respiratory distress postextubation may benefit from the application of noninvasive ventilation (38) (Level 2C). However, one trial (39) has suggested that noninvasive ventilation is not effective in this setting for a heterogeneous group of patients (few COPD patients).

SUMMARY FOR MECHANICAL VENTILATION IN COPD

- NPPV should be considered in patients presenting with a severe exacerbation of COPD (pH less than 7.30).
- Patients with milder exacerbations do not benefit from NPPV.
- NPPV should be administered in a setting that allows close cardiopulmonary monitoring.
- There is no evidence to date that supports the use of NPPV for stable COPD patients with chronic hypercapnia.
- Patients requiring conventional mechanical ventilation may benefit from pressure control ventilation.
- Heliox should be considered in patients with severe bronchospasm and high PEEP_i.
- Daily spontaneous breathing trials and a weaning protocol is strongly suggested.
- Early extubation to NPPV may be considered in a closely monitored setting.

TABLE 9
Patient selection for noninvasive ventilation

Criteria suggesting benefit	Criteria suggesting lack of benefit	Contraindications
Respiratory distress: Respiratory rate >25 breaths/min Use of accessory muscles	Milder exacerbations: pH >7.35 Mild respiratory distress	Respiratory arrest Hemodynamic instability Recent facial or gastroesophageal surgery
Respiratory acidosis: pH <7.35 PaCO ₂ >45 mmHg	Very severe exacerbations: pH <7.20 Somnolence Lack of response to NPPV Increase or no change in respiratory rate Decrease or no change in pH Excessive secretions	Craniofacial trauma Fixed nasopharyngeal abnormalities Coma

NPPV Noninvasive positive pressure ventilation; PaCO₂ Arterial carbon dioxide pressure

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LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) removes 20% to 35% of the most emphysematous lung in COPD patients. The surgery was introduced by Brantigan et al (1) in the late 1950s as a way of palliating patients with emphysema. Cooper et al (2) reintroduced the operation in 1994. In carefully selected patients, improved outcomes have been demonstrated using the stapling-excision technique and the median sternotomy approach (3) (Table 10) (Level 2B). These improvements appear to be sustained for at least three years (4). Bilateral LVRS demonstrates better results than unilateral LVRS (5) (Level 2B). Resection of lung tissue produces better results than laser ablations (6) (Level 1B).

This operation has generated an extensive debate regarding randomized clinical trials in evidence-based medicine and their relation to surgical procedures (7). The debate arises over the ethical nature of controlled trials in situations where equipoise is challenged. Before 2003, there had been five randomized clinical trials – two from the United States (8,9) and one each from Sweden (10), the United Kingdom (11) and Italy (12), all of which reported better outcomes in the surgical arms three to 12 months after surgery (Table 11). Unfortunately, these trials involved only a small number of patients (n=37 to 60) and did not include follow-up beyond 12 months. To more definitively assess the effectiveness of LVRS, three large, multicentre, randomized clinical trials were commenced: the National Emphysema Treatment Trial (NETT) (13), the Overholt-Blue Cross Emphysema Surgery Trial (OBEST) and the Canadian Lung Volume Reduction Trial (CLVRT). Of these three studies, only the NETT has been completed. This study enrolled a total

of 1218 patients with severe emphysema. All patients initially received medical therapy and underwent a pulmonary rehabilitation program for at least six weeks. During the course of the study, after the enrollment of 1033 patients, an interim analysis identified a subgroup of patients with emphysema who clearly had a higher mortality risk with LVRS (Level 1A). These were patients with an FEV₁ less than 20% of predicted and either homogeneous distribution emphysema or a diffusing capacity of no more than 20% of predicted. The enrollment criteria for the NETT was subsequently modified to exclude this population. The final results of the NETT were published in May 2003 (14). Even when the high risk group identified during the interim analysis (n=140) was excluded from the analysis, overall mortality was similar between the LVRS and medical therapy arms. At 24 months follow-up, patients who underwent LVRS had a higher likelihood of having an improved exercise capacity than patients who received only medical therapy, although the likelihood of benefit from surgery was still small (16% versus 3%, P<0.001). A posthoc regression analysis was performed to identify a subset of patients who may have experienced a mortality benefit from LVRS. Patients who had both a low postrehabilitation exercise capacity (less than 40 W for men or 25 W for women) and predominantly upper lobe emphysema were the most likely to benefit from LVRS. Two hundred ninety of the 1218 study patients were included in this subset. For patients within this subset, LVRS was associated with a significant mortality reduction (0.07 versus 0.15 deaths per patient year, P<0.005) and a greater likelihood of exercise improvement (30% versus 0%, P<0.001). Thus, based on the findings of the NETT, it seems that LVRS may offer a benefit for COPD

TABLE 10
Selection criteria for lung volume reduction surgery

Indications	Contraindications
Disability from emphysema (not from bronchitis or asthma) despite maximal medical treatment	Comorbid disease, ie, operation-prohibitive risk or life expectancy < two years
Age <75 to 80 years	Severe obesity or cachexia
Abstinence from smoking > four months	Severe coronary artery disease
FEV ₁ <40% of predicted	Active smoker
Total lung capacity >120% of predicted	Alpha-1-antitrypsin deficiency
Respiratory volume >175% of predicted	Extensive pleural symphysis
Hyperinflation, preferably with upper lobe dominance by computerized tomography scan (heterogeneous distribution)	Chest wall deformity
	PaCO ₂ >50 to 60 mmHg
	PAP >35 mmHg (mean)
	FEV ₁ ≤20% of predicted and homogeneous distribution or DLCO <20% of predicted

DLCO Carbon monoxide diffusing capacity; FEV₁ Forced expiratory volume in one second; PaCO₂ Partial pressure of arterial carbon dioxide; PAP Peak airway pressure

TABLE 11
Summary of outcomes from randomized controlled trials for lung volume reduction surgery (LVRS)

	FEV ₁	FVC	RV	TLC	ABG	6 MWD	QOL	Survival
Criner et al (8)	*	*	*	*	*	†	*	Not reported
Goodnight-White et al (9)	*	Not reported	Not reported	Not reported	Not reported	*	Not reported	‡
Lofdahl et al (10)	*	Not reported	*	Not reported	Not reported	Not reported	*	Not reported
Geddes et al (11)	*	†	*	*	†	†(shuttle test)	*	†
Pompeo et al (12)	*	Not reported	*	Not reported	*	*	Not reported	Not reported

*Statistically significant difference detected between LVRS group and control group; †No statistically significant difference detected between LVRS group and control group; ‡Numbers too small for statistical analysis. Six-month overall mortality was 4% in LVRS group versus 17% in control group. 6 MWD Six minute walking distance; ABG Arterial blood gas; FEV₁ Forced expiratory volume in 1 s; FVC Forced expiratory vital capacity; QOL Quality of life; RV Respiratory volume; TLC Total lung capacity

patients with a combination of upper lobe emphysema and low exercise capacity. However, these conclusions are based on a posthoc analysis and would require prospective validation.

KEY MESSAGES

- Patients with FEV₁ less than 20% predicted and either homogeneous emphysema or carbon monoxide diffusing capacity less than 20% predicted clearly do not benefit from LVRS.
- Patients with predominantly upper lobe emphysema and low exercise capacity are most likely to benefit from LVRS, but more definitive studies are required.

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LUNG TRANSPLANTATION FOR COPD

Lung transplantation is an excellent option for certain carefully selected patients with advanced COPD (Level 3A). Over 12,000 lung transplants have been performed to date, with COPD accounting for approximately 60% and 30% of the single and bilateral procedures, respectively (1). Anticipated survival rates following lung transplantation for all disease states are in the range of 75% at one year and 50% at five years (1); however, recipients with COPD appear to have better outcomes than those with other conditions (Level 3B). Whether improved outcomes can be achieved with the use of bilateral procedures compared with single lung transplantation is controversial at present (2). Chronic graft dysfunction associated with obliterative bronchiolitis, thought to be a manifestation of chronic rejection, is the major complication affecting long-term morbidity and mortality (3), and is present in at least one-half of long-term survivors.

It is important to recognize that, in contrast with patients with cystic or pulmonary fibrosis, a survival advantage with lung transplantation has not clearly been demonstrated for all patients with COPD (4,5) (Level 3C). Unfortunately, prospective studies examining which patients are most likely to benefit are lacking. Recently drafted international guidelines for the selection of COPD patients who may be appropriate candidates for consideration for lung transplantation emphasize the need for optimization of medical therapy (including pulmonary rehabilitation), as well as consideration of LVRS in appropriate individuals (6). Patients with COPD are considered to be potentially in the transplant window if they meet the following criteria: FEV₁ less than 25% predicted (without reversibility) and/or PaCO₂ greater than 55, and/or elevated pulmonary artery pressures with progressive deterioration, such as cor pulmonale (Level 3B). The authors note that preference should be given to those patients with elevated PaCO₂ with progressive deterioration who require long-term oxygen therapy, because they have the poorest prognosis (6).

Lung transplant recipients can achieve substantial improvements in exercise capacity (7) (Level 2A), and the great majority of recipients are free of supplemental oxygen. The limited data available to date indicate that these patients also attain important improvements in HRQoL (8) (Level 2A). Over 80% of lung transplant recipients surviving more than

five years report no activity limitation, and almost one-half of American lung transplant recipients are working five years following the procedure (1). Little information is available examining other important outcomes including cost effectiveness of the procedure, quality-adjusted life years, etc.

Currently, the number of potential lung transplant recipients far outstrips the donor supply (9), a reality that will continue to limit the widespread use of lung transplantation for treatment of advanced respiratory diseases. A number of strategies targeting expansion of the donor pool may prove helpful in the near future, including improvement of donor identification, increased use of marginal donors, living lobar lung transplantation and xenotransplantation. The uncertainty with respect to which COPD patients derive the greatest benefit from lung transplantation (both in terms of survival and quality of life) emphasizes the need to develop validated selection criteria. Consideration should be given to the development of a prospective randomized trial comparing lung transplantation with optimal medical therapy (including structured pulmonary rehabilitation) in patients with advanced COPD, with attention to meaningful health outcomes including survival, quality of life and cost effectiveness.

KEY MESSAGES

- Lung transplantation is an excellent option for certain carefully selected patients with advanced COPD.
- Obliterative bronchiolitis is the major complication affecting long-term morbidity and mortality.
- A survival advantage with lung transplantation has not clearly been demonstrated for all patients with COPD.
- Prospective studies examining which patients are most likely to benefit are lacking, but major indications include FEV₁ less than 25% predicted and/or PaCO₂ greater than 55, and/or cor pulmonale with progressive deterioration.
- Lung transplant recipients can achieve substantial improvements in functional capacity.
- The number of lung transplants is limited by the modest donor supply.
- Validated selection criteria need to be developed to help determine which COPD patients derive the greatest benefit from lung transplantation.

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GUIDELINES FOR MANAGEMENT OF ALPHA-1-ANTITRYPSIN DEFICIENCY

Alpha-1-antitrypsin (AAT) deficiency and its association with emphysema were first discovered in the early 1960s by Laurell and Eriksson (1). AAT (also termed alpha-1-protease inhibitor) is the major component of serum alpha-1-globulin, the major antiprotease in plasma; its primary function is considered to be inhibition of neutrophil elastase. AAT is encoded by a single gene on chromosome 14 (2) and is synthesized by the liver cells, secreted into the plasma, and diffused passively into the lung interstitium and alveolar lining fluid. The AAT phenotype is determined by the expression of two codominant alleles classified under the protease inhibitor (Pi) system (3,4). The normal AAT phenotype is MM, while severe deficiency is mostly associated with the ZZ phenotype, with AAT serum levels of about 15% of normal (2). The Z phenotype results from a single amino acid substitution of 342 glutamine to lysine (5). As the result of this single substitution, there are conformational changes in the molecule resulting in the polymerization of the protein, and preventing its secretion by the hepatocyte (6).

The heterozygote state (Pi MZ) occurs in approximately 2% to 3% of the white population and results in AAT levels about 50% to 70% of normal. The MZ heterozygote state may predispose to the development of COPD in smokers, although the epidemiological evidence is not consistent (7-10,11). Another common variant is the slow mobility (S) allele, which results in AAT levels of approximately 80% of normal but is not known to be associated with an increased risk for COPD (12).

Smokers with severe AAT deficiency are likely to develop disabling COPD in their early 40s (3). Severe deficiency in Pi ZZ individuals occurs in about 95% of cases; in rare cases, severe deficiency is due to homozygous alleles, resulting in nondetectable plasma AAT ('null' alleles). Null homozygotes are at very high risk for the development of emphysema, greater than that of Pi ZZ. In AAT deficiency, panacinar emphysema is the predominant lesion and characteristically has a basal predominance. Symptoms of chronic bronchitis may also be present in 20% to 60% of patients (3). Nonsmokers with AAT deficiency rarely develop respiratory symptoms before the age of 50 years, but they may have mild impairment of FEV₁ in their sixth or seventh decade. Exposure to occupational or environmental pollutants may further predispose to the development of COPD. It is likely that impaired lung function is also related to other inherited factors that have yet to be characterized. This is suggested by the finding that Pi ZZ individuals, detected in family screening of AAT-deficient emphysema patients, have more impairment in lung function than Pi ZZ subjects discovered in screening studies of the general population (13,14).

Emphysema is thought to result from an imbalance between elastases released in the lung and protective antiproteases normally present in the lung parenchyma (15). An imbalance favouring elastases leads to proteolytic damage to lung connective tissue, elastin degradation and emphysema. The imbalance that arises from the inherited deficiency of AAT is exaggerated if tobacco smoke simultaneously increases the release of neutrophil elastase in the lung. The aim of antitrypsin replacement therapy is to correct this protease-antiprotease

imbalance and prevent or slow down the progression of emphysema.

Severe AAT deficiency can also lead to liver disease and the development of cirrhosis (16). The abnormal Z AAT is retained and polymerized in hepatocytes, which may lead to hepatic injury and cirrhosis (6,17). This subject is further reviewed in the recent position statement of the CTS and three other review papers (3,4,6,12).

Targeted testing for AAT and Pi typing

There is recent evidence that suggests that screening for AAT deficiency in unselected patients with lung diseases (including COPD, emphysema and asthma) does not detect a significant number of individuals with AAT deficiency compared with the general population (18). However, all physicians are urged to perform targeted testing on selected individuals for AAT deficiency. The CTS AAT guidelines (12) suggest that any patient with atypical features of COPD, including patients with early onset disease and/or a positive family history, be tested for AAT deficiency and AAT phenotype (Pi type). All provincial health plans should cover the cost of this testing. Referral to a respirologist is strongly recommended for patients with AAT deficiency (12).

AAT registries

The CTS position statement (12) strongly recommends participation in the Alpha-1 Canadian Registry (Web site <www.alpha1canadianregistry.com>; telephone 1-800-352-8186), which was established in 1999 under the auspices of the CTS and in collaboration with the Alpha-1 International Registry (AIR). The international registry currently gathers existing medical information about people who are deficient in the protein to better understand why some people remain healthy and free of lung disease, and why some people develop emphysema. In the longer term, people who are in the registry may be asked if they are willing to participate in research trials that might lead to improved diagnosis, assessment and management of this disease. By coordinating research efforts at this international level, the registry scientists hope to make more rapid progress than individual scientists could achieve working in isolation. In addition to providing the opportunity to better understand the disease, this also allows Canadian scientists to more readily participate in international efforts. In the United States, the Alpha-1 Research Registry (Web site <www.alphaoneregistry.org>; telephone 1-877-886-2383) was formed in 1996 in response to the closing National Heart, Lung and Blood Institute Registry. The Alpha-1 Research Registry aims to facilitate alpha-1 research by providing investigators with patients and groups willing to participate in the research.

AAT replacement therapy

Antitrypsin replacement therapy (19) became available for prescription use in the United States and Canada in 1989. Standard therapy requires weekly infusions of a purified antitrypsin preparation (Prolastin, Bayer, USA) at a dose of 60 mg/kg (20). Monthly infusions of 250 mg/kg (21) and biweekly infusions of 120 mg/kg (21,22) have also been used. Replacement therapy partially corrects the biochemical defect

by raising serum levels of antitrypsin above a theoretically protective threshold level of 0.8 g/L (20-22). This level has been regarded as adequately protective, based on the observation that subjects with moderate AAT deficiency (SZ phenotype) who exceed this level appear not to be at a significantly increased risk for the development of emphysema (19). The aim of antitrypsin replacement therapy is to reduce the excessive decline in lung function that these patients experience; replacement therapy is not expected to improve already impaired lung function (19).

Prolastin received regulatory approval in North America after clinical trials demonstrated that regular intravenous therapy with the purified blood product partially and safely corrected the abnormally low levels of AAT typically found in the plasma and bronchoalveolar lavage fluid of deficient individuals. The American Thoracic Society published its guidelines for AAT replacement therapy (19) in 1989, which recommended replacement therapy for severely deficient individuals with evidence of significant obstructive lung disease, provided that patients had quit smoking and were receiving optimal medical therapy. More recently, the CTS subcommittee on AAT deficiency issued an updated position statement regarding AAT replacement therapy (23). After careful review of the studies evaluating the effect of AAT replacement therapy (24-26), the subcommittee concluded that replacement therapy remained an unproven treatment, but that there was evidence suggesting benefit to patients with an FEV₁ of 35% to 65% predicted (12). The CTS recommended restricting the option of AAT replacement therapy to AAT-deficient patients with FEV₁ greater than 35% and less than 50% predicted, who have quit smoking and are on optimal medical therapy, but yet continue to show a rapid decline in FEV₁ (greater than 80 mL/year) (23). It is recommended that the annual decline in postbronchodilator FEV₁ be determined in stable patients on standard COPD therapy, at intervals of three to six months for at least 18 months (preferably two years). Replacement therapy is recommended for treating all of the rare null homozygotes.

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International clinical trial

There is growing international consensus surrounding the need for, and feasibility of, a randomized controlled trial to assess the efficacy of replacement therapy (27,28). Implicit in this recommendation would be the availability of sufficient purified AAT (by requiring that Canadian blood products be available for the production of purified AAT) and the assurance of adequate funding to perform this multinational trial.

KEY MESSAGES AND RECOMMENDATIONS

- Severe AAT deficiency predisposes susceptible individuals to the development of emphysema (especially among smokers) (Level 2A).
- Targeted testing for level of AAT deficiency and AAT phenotype (Pi type) should be performed in any patient with atypical features of COPD, including patients with early onset disease, a positive family history, and who become disabled in their early 40s or 50s (Level 3A).
- Referral to a respirologist for patients with AAT deficiency is strongly recommended (Level 3A).
- Participation in the Alpha-1 Canadian Registry, the Alpha-One International Registry and the National Heart, Lung and Blood Institute Registry is strongly encouraged (Level 3A).
- AAT replacement therapy (Prolastin) should be restricted to AAT deficient patients with FEV₁ over 35% and less than 50% predicted, who have quit smoking and are on optimal medical therapy, but yet continue to show a rapid decline in FEV₁ (more than 80 mL/year) (Level 2B).
- Replacement therapy is also recommended for treating rare null homozygotes because they have no detectable AAT and an accelerated rate of decline in lung function (Level 3B).
- An international randomized clinical trial should be conducted to more accurately determine the overall efficacy of replacement therapy (Level 3A).

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END-OF-LIFE CARE IN COPD

Despite the importance of COPD in terms of its prevalence, its impact on HRQoL, and its impact on the manner of patient death, "no statement exists from any professional organization pertaining to ethical issues unique to this patient population" (1), and no authority or body has published guidelines to assist patients or their caregivers to deal with death from COPD.

Reflecting the 'death denying' culture in which we live, most individuals living with advanced COPD have not been given (2,3) or have not taken the opportunity (4) to clearly articulate their wishes for the level of care they wish to receive as COPD progresses to its late stages. There are few descriptions of the experiences of COPD patients as they have approached the end of their lives (5). An understanding of these experiences and the provision of opportunities for patients to express their concerns and fears should assist them, their families and their health caregivers to plan more positively for 'what to expect' towards the end of their lives.

Unfortunately, accurate predictions for individual patients cannot be made regarding functional status and quality of life, rates of short and long-term survival, and length of hospital stay. However, there are good outcome studies (6-10) of hospital admissions for COPD that can provide guidance to both caregivers and patients involved in the decision-making process.

Patient perspectives

Patient fears and desires for information about COPD, advance directives and life support: A desire to improve the care of patients with COPD implies that physicians should commit to listening to what patients tell them and act on this information. COPD patients have indicated the skills they think physicians need to provide end-of-life care (11). The most important skills were the ability to provide emotional support, to communicate, to be accessible and to provide continuity of care. In addition, it was important for physicians to provide information in five areas: diagnosis and disease process, treatment, prognosis, what dying might be like, and advance care planning (11). In contrast, sources of major dissatisfaction described by patients with end stage COPD in a United Kingdom study (12) included perceptions of inadequate provision of information about their illness, its management and the type of social help available. Many patients with COPD felt that they did not have enough information about their own prognosis and future management, and 26% did not know that their disease was fatal (12). Much patient information was derived from sources other than their primary caregiver.

In the psychosocial arena, COPD patients describe fear of isolation and of how they might die (13). They fear increasing dyspnea and live in "the shadow of fear and uncertainty cast by their near death experiences" (5). While nearly all patients in a rehabilitation program wanted information and a patient-physician discussion about advance directives and mechanical ventilation, these discussions had actually taken place for only 19% and 15% of patients, respectively (4).

Functional status, quality of life and quality of death: Several factors are potential determinants of functional status in COPD: severity of airflow obstruction, gas exchange

abnormalities, frequency and severity of acute exacerbations, age, comorbidities and social supports (14).

There is ample evidence that the quality of life for COPD patients is poor (15,16). In COPD patients hospitalized with severe exacerbations, HRQoL was worse than for survivors of cardiopulmonary resuscitation (16). In a comparison of patients with non small cell lung cancer and COPD (12), those with COPD self-reported lower scores for activities of daily living, lower levels of social and physical functioning (social isolation is common in COPD) and more depression. Patients with cancer tend to die in noncritical care settings with good symptom control (17), while COPD patients often die in the ICU, receiving technically assisted support with reports from surrogates of poor symptom control.

Physician perspectives

What do physicians discuss with their COPD patients? A survey of Canadian respirologists clearly demonstrated that end-of-life discussions often occur too late and do not meet the expectations of patients. For example, when discussing mechanical ventilation, more respondents indicated that these discussions would take place in the ICU than in the clinic or office, and 84% of respondents waited until dyspnea was severe (3). Biases held by physicians influenced whether they recommended mechanical ventilation (3). Physicians need to be aware that the way they frame their discussions influences patient choices (18).

What can physicians do to improve end-of-life care for COPD patients? Curtis (19) describes three general phases to discussions about end-of-life care for patients: making preparations, holding discussions and finishing discussions. The key elements appear in Table 12. In addition to reviewing these elements in comparison with their own practices, physicians specifically caring for patients with COPD should consider other key aspects of end-of-life care and encourage discussions about the following:

- Patient fears;
- The extent of family and other local support systems;
- Preferences for where the patient will die (hospital, hospice, at home);
- Use or nonuse of mechanical or noninvasive ventilation versus comfort measures with the next exacerbation of COPD; and
- Whether and when to involve palliative care services.

The importance of kindness and availability cannot be overemphasized.

Who should be involved in end-of-life discussions and care? End-of-life discussions should not be deferred until, or only conducted in, the ICU unless absolutely necessary. Although the primary care setting is a far better alternative, general practitioners in the United Kingdom initiate these discussions less often with COPD patients than with others, and feel ill-prepared for these discussions (20).

Pulmonary rehabilitation programs may be a suitable venue for end-of-life discussions with COPD patients. However, while most pulmonary rehabilitation programs (4,21) considered their own program an appropriate site for education about

TABLE 12**Discussions about end-of-life care****1. Making preparations before a discussion about end-of-life care**

Review previous knowledge of the patient and/or family
 Review previous knowledge of the patient's attitudes and reactions
 Review your knowledge of the disease: prognosis, treatment options
 Examine your own personal feelings: attitudes, biases and grieving
 Plan the specifics of location and setting: a quiet, private place
 Have advance discussion with the patient or family about who will be present

2. Holding a discussion about end-of-life care

Introduce everyone present
 Set the tone in a nonthreatening way: "This is a conversation I have with all my patients..."
 Find out what the patient or family understands
 Find out how much the patient or family wants to know
 Be aware that some patients do not want to discuss end-of-life care
 Discuss prognosis frankly, in a way that is meaningful to the patient
 Do not discourage all hope
 Avoid temptation to give too much medical detail
 Make it clear that withholding life-sustaining treatment is NOT withholding care
 Use repetition to show that you understand what the patient or family is saying
 Acknowledge strong emotions and use reflection to encourage patients or families to talk about these emotions
 Tolerate silence

3. Finishing a discussion about end-of-life care

Achieve common understanding of the disease and its treatment issues
 Make a recommendation about treatment
Ask if there are any questions
 Ensure basic follow-up plan and make sure the patient and/or family know how to reach you for questions

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advance directives, most did not provide this educational component.

Another approach is to establish formal links with palliative care programs. Palliative care can be defined as a holistic approach to the alleviation of symptoms and suffering when curing or reversing the underlying disease process is not possible (22). This approach to medicine is especially relevant for COPD patients at the end-of-life. However, until access to formal palliative care services becomes more readily available across Canada, family physicians and respirologists will continue to provide the bulk of care to dying COPD patients, usually without the assistance of palliative care specialists.

Empirical data that should inform end-of-life discussions with COPD patients

Hospitalization outcome data: Outcomes of admissions due to AECOPD have been quantified (6,8). In the United States (6), investigators examined hypercapnic exacerbations of COPD. The mortality rate was 11% for the index admission and 43% at one year. Mortality increased with age, severity of the initial exacerbation, comorbidities, evidence of malnutrition, poor performance status and number of readmissions. Similar results were gathered in a large British population

hospitalized for exacerbations (8). Age was the most consistent predictor of death in the British study. In two other studies (7,23) of survival subsequent to discharge of 270 and 362 patients, median survivals were reported as 3.1 years and 224 days, respectively. Age and presence of comorbidities again proved to be predictors of death. In the British study (8), a bed-bound status before hospital admission increased the risk of death by a factor of 20. The investigators recommended recording functional status when patients are admitted to hospital with AECOPD.

One admission predicts subsequent admissions. In the British study (8), 34% of patients with COPD were readmitted to hospital within three months of the index admission, and in the American study, 50% of those who survived the initial admission were readmitted over the next six months. During the last six months of life, patients dying with COPD spent 15% to 25% of their remaining time in hospital (16). This is in keeping with data from Ontario, indicating that the majority of COPD patients who die do so in hospital (24).

The above indicates that hospital admission for an exacerbation of COPD is a potentially ominous event.

Predictors of survival in stable COPD: Initial FEV₁ and age were the most important predictors of survival in one large series of COPD patients (25). Low body mass index (26-28) and low PaO₂ (27) were additional significant independent predictors of increased mortality.

While applicable to large groups of stable patients with COPD, these risk factors do not allow for accurate predictions of mortality in individual patients. However, these health determinants should be considered during discussions of prognosis with patients.

Symptom management

Respiratory symptom management: In Table 13, the recommendations for pharmacological agents beneficial in providing nonspecific respiratory symptom control, as described by Heffner (with permission) (29), are summarized.

Dyspnea is the dominant symptom of COPD, and in severe disease, it is present on trivial exertion or at rest. It is the overriding complaint affecting quality of life (16). All patients with advanced disease should be considered for nonspecific palliative measures to relieve dyspnea. Simple measures such as directing cool air onto the face with a fan, changing body position and teaching patients to pace themselves can effectively reduce dyspnea (30,31).

Psychological factors such as anxiety, fear and panic frequently play an important role in heightening dyspnea in COPD (32). Anxiety can often be alleviated by clarification of the cause of dyspnea and treatment options available. Relaxation techniques and breathing retraining should be taught to patients, for use during panic attacks. When non-pharmacological measures have failed to control anxiety and panic attacks, anxiolytic medications may be helpful; however, studies have yielded conflicting results (31,32).

The benefit of long-term oxygen use on survival, hemodynamics and neurocognitive function in hypoxemic COPD patients is well established (33-35). However, the role of oxygen in palliation of dyspnea in mildly hypoxemic advanced COPD has not yet been adequately investigated. Without

further study, the routine use of oxygen for dyspnea palliation in COPD patients without severe hypoxemia cannot presently be justified.

Opioids reduce dyspnea and ventilation in COPD in response to a variety of stimuli, including exercise and blood gas abnormalities (36). Respiratory depression is an uncommon clinical problem (tolerance develops quickly) if patients are initiated on a low dose and titrated slowly. Potential problems notwithstanding, physicians have a duty to relieve the burden of distress experienced by dyspneic patients with severe COPD, and opioid medications should be considered for dyspnea palliation in the terminal stages of COPD.

Comfort medication may also need to include medications to reduce distress secondary to retained respiratory secretions and cough (Table 13) (29).

Depression in severe COPD: Patients with COPD are often depressed (37). Lacasse et al (38) demonstrated that 57% of a sample of severe, oxygen-dependent COPD patients reported depressive symptoms and 18% were judged to be severely depressed. Depression can heighten patients' awareness of physical symptoms. The diagnosis of depression is hindered by underdiagnosis, undertreatment due to fear of side effects, and lack of timely referral to appropriate psychological experts and community resources (32).

Palliative noninvasive ventilation: The introduction of noninvasive ventilation for COPD has had a major impact on outcomes for patients with acute exacerbations (39). There is also evidence that in the chronic setting, quality of life improves significantly with the use of noninvasive ventilation in severe COPD (40,41). In the palliative phase, there are no controlled trials demonstrating that noninvasive ventilation provides more comfort than medical management alone (ie, use of opioids and benzodiazepines). Two uncontrolled trials have suggested that noninvasive ventilation can reduce dyspnea and preserve patient autonomy in well selected patients (42,43). The goals of care need to be clearly articulated and agreed on by patients, families and their caregivers, and the rationale for providing any technically-assisted support, including noninvasive ventilation, should be grounded firmly in the need to provide comfort. A positive short-term response should be demonstrated, and decisions regarding end-of-life care should be made before noninvasive ventilation is instituted, in case it fails to provide comfort (44). Given these considerations, there may be a time-limited role for palliative noninvasive ventilation as the end-of-life approaches.

Caregiver burden

The current trend in health care is to shift the provision of patient care from the hospital or clinic setting to the home. This can add to the substantial burden that caregivers already experience when supporting a family member with advanced chronic disease such as severe COPD. The impacts on family caregivers can be broadly divided into three categories: physical demands of providing direct care, emotional demands of supporting a loved one with a chronic or terminal illness, and financial expense (29). Reductions in caregiver burden may be achieved by a team-managed, home-based, primary care model (45).

TABLE 13
Agents used to manage symptoms related to chronic obstructive pulmonary disease at the end of life (29)

Indication	Drug	Commonly used dosage
Dyspnea	Morphine	
	Oral	5 mg to 10 mg q4h
	Rectal	5 mg to 10 mg q4h
	IV, SQ or IM	Titrate to relieve dyspnea
	Nebulized	5 mg in 2 mL normal saline q4h with handheld nebulizer
	Benzodiazepines	
	Lorazepam, oral, sublingual, IV	1 mg to 2 mg q1-4 h
	Diazepam, oral, IV	2.5 to 25 mg daily
	Midazolam, SQ	5 mg to 10 mg SQ, then 10 mg to 30 mg continuous SQ infusion for two days
	Other	
	Chlorpromazine IV	12.5 mg IV q4-6 h
	Chlorpromazine, rectal	25 mg q4-6 h
Cough	Opioids	
	Codeine, oral	30 mg to 60 mg q4h
	Morphine, IV	2.5 mg to 5 mg q4h
	Inhaled anesthetics	
Bupivacaine, 0.25%	5 mg q4-6 h	
Retained secretions	Anticholinergic agents	
	Scopolamine, SQ	0.4 mg to 0.6 mg q4-6 h
	Scopolamine, transdermal patch	q72h
	Hyoscyamine, SQ	0.25 mg to 0.5 mg q4-6 h
	Atropine, SQ	0.4 mg q4-6 h

IM Intramuscular; IV Intravenous; SQ Subcutaneous

Useful instruments and discussion aids

Decision guides: Dales et al (46) have described the use of a decision guide for patients with COPD. Larger studies are required as understanding of the needs of patients with advanced COPD improves.

Advance directives: Some of the data reviewed in the first section of this paper clearly underscore the gap between patient desires for physician-initiated discussion about end-of-life issues and the low incidence of physician response to this need. An advance directive should, at the very least, improve the likelihood that patients will receive the levels of care that they would like when they are unable to make these decisions for themselves. None of the barriers to advance directives are insurmountable. All can be addressed if the desire is there. Plans need to be subject to ongoing review, including an understanding of the rigidity or flexibility of such directives in specific circumstances (1). Martin et al (47) have provided a useful overview of advance care planning in general. There is little to lose by broaching the subject of end-of-life care in all patients with severe COPD. Physicians need to be more proactive and take a lead in addressing the realities of end stage COPD so that their patients will become better informed and confident that they will not be abandoned in the end.

Summary

1. There is considerable discordance between patients' wishes and expectations for information about their disease and its prognosis, and what physicians provide.
2. There is a need to improve understanding of patients' experiences and needs through well timed, honest, informative, empathetic but realistic conversations that can form the basis of effective advanced care planning.
3. Discussions about end-of-life issues often occur too late, are held in inappropriate settings such as the ICU and do not meet the expectations of patients.
4. Lack of access to formal palliative care services or pulmonary rehabilitation programs means that family physicians and respirologists must have discussions with and provide the bulk of end-of-life care to COPD patients.
5. Mortality during admission with exacerbation of COPD ranges from 10% to 20%. Unfortunately, it remains difficult to predict outcome in individual patients.
6. Predictors of survival in stable COPD are well established but of little value in individual patients.
7. Patients with COPD spend progressively more time in hospital toward the ends of their lives.
8. Both pharmacological and nonpharmacological treatments are available to assist in the palliative management of distressing respiratory symptoms, especially dyspnea.
9. Emotional consequences of living with severe COPD include anxiety, fear, panic and depression. These psychological factors can impose an additional barrier to effective symptom control, can further reduce quality of life and also require pharmacological and nonpharmacological treatment strategies for effective management.
10. Noninvasive ventilation may provide some symptom relief in COPD patients who otherwise would not accept intubation and mechanical ventilation.
11. Caregiver burden is likely substantial but is largely unmeasured for COPD.
12. Decision aids may assist patients when considering intubation and mechanical ventilation.
13. Informed discussions among patients, families and physicians regarding advance directives should improve the likelihood that patients will receive the levels of care that they would choose.

KEY RECOMMENDATIONS**Patient education**

1. COPD patients should be encouraged to articulate to their physicians and caregivers a desire for information about their disease, prognosis and possible circumstances of their death (Level 2A).

Professional education

2. All physicians who care for COPD patients should possess the necessary skills to conduct discussions with their patients about end-of-life issues (Level 2A).

3. Family physicians and respirologists require further education to help them identify which COPD patients would benefit most from timely discussions about end-of-life issues (Level 2A).
4. Physicians require increased education about how to incorporate pharmacological and nonpharmacological treatments to achieve optimum symptom control in severe COPD (Level 3B).

Health policy issues

5. Better access to palliative care services for clinicians providing care to COPD patients is required (Level 3B).
6. For patients admitted to hospital, physicians should consider whether changes to institution policies and procedures (eg, use of admission standing orders) would help to identify hospitalized COPD patients at risk of dying; and systematically ensure that discussions regarding end-of-life care take place between clinicians and hospitalized COPD patients (Level 2B).

Research priorities

7. The role of noninvasive ventilation in palliation of dyspnea in COPD patients with chronic respiratory failure who otherwise would not accept intubation and mechanical ventilation is a priority (Level 3B).
8. Research into the likely substantial but largely unknown impact of COPD on caregiver burden should be encouraged, particularly that involving the development of validated measurement tools (Level 3B).
9. Development and validation of a Canadian population of COPD-specific quality of life questionnaire is required to improve prediction of hospitalization and mortality for patients with COPD (Level 2A).
10. Further development and validation of decision aids are needed to assist patients and their caregivers in making end-of-life decisions (Level 2A).

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FUTURE THERAPIES IN COPD

A number of novel therapies have been developed to suppress the inflammatory process in the hope of modifying disease progression in COPD (1-3). Experimental therapies include inflammatory mediator antagonists such as leukotriene B₄ inhibitors, tumour necrosis factor inhibitors, chemokine inhibitors, antioxidants and prostanoic inhibitors. Other anti-inflammatory therapies in development include phosphodiesterase type 4 inhibitors, interleukin-10, mitogen-activated protein kinase inhibitors and adhesion molecule blockers. New antineutrophil therapies under investigation include prostaglandin E₂ and colchicine.

Metalloproteinases are released from inflammatory cells in the lung in COPD and are thought to play an important role in its pathogenesis. Protease inhibitors and metalloproteinase inhibitors may favourably modify the inflammatory response and prevent progression.

New mucoregulators, which reduce mucous hypersecretion and improve mucociliary clearance, also have the potential to improve airway dysfunction in COPD. Finally, animal studies have recently shown that the agent retinoic acid may reverse proteolytic destruction and help stimulate growth of damaged alveoli.

Phosphodiesterase type 4 inhibitors

These agents are currently being clinically evaluated in COPD. They combine anti-inflammatory and bronchodilator effects and have been shown in preliminary studies to improve lung function, comparable with that of existing bronchodilators (4-6). No information is available as to whether these drugs (cilomilast, roflumilast) delay the rate of progression of the disease.

FUTURE RESEARCH QUESTIONS AND SUGGESTIONS

Screening

- Does targeted screening of symptomatic smokers or ex-smokers improve overall outcomes in COPD?
- Is the brief COPD test suggested by the panel (see clinical assessment section) valid and useful in clinical practice?
- Does spirometry augment smoking cessation interventions?

Disease stratification and differential diagnosis

- Is the proposed stratification system, based on the MRC scale, of clinical use?
- There is a need to develop and test stratification systems that incorporate measures of impairment, disability and handicap.
- There is a need to develop better criteria to distinguish COPD from asthma, both clinically and in the laboratory (ie, biomarkers).

Disease subgroups

- Is it possible to identify discrete disease subgroups in COPD by clinical and laboratory measures?

- Do such subgroups vary in their response to therapeutic interventions and in their natural history?

Natural history of COPD

- There is a need to conduct large population-based studies to delineate the natural history of COPD using a variety of relevant parameters, both clinical and biological.

Assessment

- Does a more comprehensive assessment of COPD patients lead to better clinical outcomes?

Management

- What type of educational programs work best for COPD patients and what outcomes best evaluate this?

Pharmacotherapy

- Are the effects of combined long-acting bronchodilators (anticholinergics and LABAs) superior to each agent alone in terms of mechanics, exercise capacity, exacerbation reduction and improved quality of life?
- Does the addition of ICS to patients maximally bronchodilated with long-acting anticholinergics and beta-2-agonists convey additional improvements in mechanics, dyspnea, exercise tolerance, exacerbations and quality of life?
- What criteria should be used to define clinical responses to ICS and systemic steroids?
- What should be the sequence of introduction of bronchodilators and inhaled steroids in a given patient?
- What is the effect of inhaled steroids on inflammatory markers in COPD in the long term?

Acute exacerbations

- What is the pathophysiology of AECOPD?
- What are the relative roles of steroids and antibiotics?
- There is a need to compare the effects of first-line and second-line antibiotics in the treatment of purulent exacerbations of less severe COPD.
- What are the factors that predict a poor outcome during AECOPD?
- What are the criteria to identify patients with exacerbations requiring hospitalization?
- In a nonpurulent exacerbation, what is the effect of steroids in patients with different levels of disease severity?
- What is the role of ICS and oral steroids in mild, simple AECOPD?
- Is there a role for high dose ICS in AECOPD?
- What is the role of action plans in the management of AECOPD? Are they effective?

Pulmonary rehabilitation

- There is a need to study the effects of strength and endurance training on both the short-term and long-term outcomes of COPD.

- What is the role of community-based programs in maintaining the results of short exercise training programs?
- What is the cost effectiveness of rehabilitation programs when added to smoking cessation programs?
- There is a need to study the effects of various interventions (eg, nutrition, anabolic steroids, growth hormone analog) on peripheral muscle function and exercise capacity in COPD.
- There is a need to study the effects of chronic hypoxia on peripheral muscle function in COPD.
- There is a need to better understand cardiopulmonary interactions during exercise in COPD.

Oxygen

- What is the role of oxygen therapy in patients who only desaturate during exercise?
- What exercise test best identifies an oxygen responder?
- What is the role of ambulatory oxygen as an adjunct to exercise training in COPD?
- What is the role of oxygen therapy on the long-term outcomes of patients who demonstrate isolated nocturnal desaturation?
- What is the impact of combined COPD and sleep apnea on morbidity and mortality in COPD?
- What is the efficacy of noninvasive ventilatory support in patients with coexistent obstructive sleep apnea and COPD?

Clinical trial outcomes

- What are the clinically significant changes in the TDI and in various health status questionnaires following therapeutic interventions in COPD?

End-of-life research

- Studies are required to determine the definitive role of opioid therapy, supplemental oxygen therapy and

noninvasive ventilatory assistance on the symptoms and quality of life in patients with end-stage COPD.

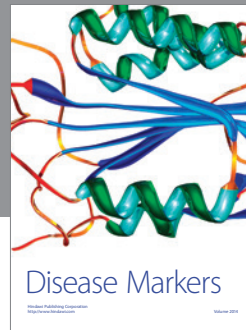
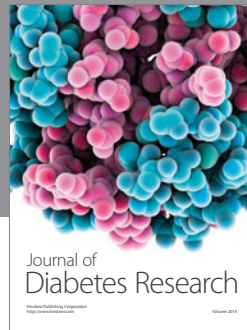
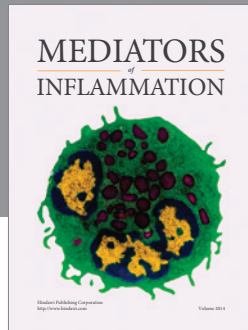
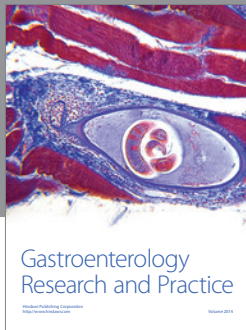
- What are the caregiver and economic burdens for end-of-life care of the COPD population in Canada?

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